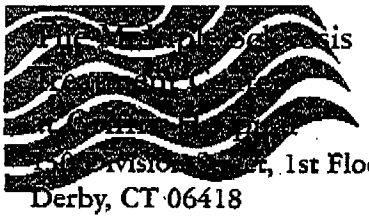

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Joseph B. Guarnaccia, M.D., L.L.C., Director

January 14, 2014

RE: Michael Wenger
DOB: 8-11-1959

To Whom it May Concern;

This letter is in response to your request for a written statement regarding Michael Wenger, who has been my patient with multiple sclerosis since his diagnosis in May of 2006. Based on my treatment of Mr. Wenger for over the last 7 years, it is my opinion that he has been totally disabled since September 25, 2009 from his previous occupation as a Vice President of technology at NASDAQ as well as from any other occupation for which he may otherwise be suited as a result of his MS symptoms, including visual and cognitive deficits. He has been totally compliant with follow up visits, numbering several times a year, and with his treatment plan.

Medical History

In May of 2006, he presented with sudden inability to read and put words together and visual loss in the right eye. On questioning, he mentioned that during the past year he had two episodes of left leg weakness and numbness. His examination revealed a dense visual field defect on the right, numbness and ataxia. A neuropsychological examination was not performed. His MRI revealed a left subcortical lesion involving the basal ganglia, which showed contrast enhancement. Although he received a standard course of intravenous steroids, his symptoms persisted and new symptoms appeared, including fatigue, tinnitus and vertigo. A repeat MRI scan showed a potential new lesion in the right temporal lobe of the brain. That June, he complained of poor recall, inability to work full time, and left arm pain, which was sometimes severe. He also described attacks of yawning, up to 30 times per hour and a "buzzing sensation" in his head. Because of these persistent symptoms he was treated with plasma exchange, interferon beta 1a (Rebif) as well as chemotherapy (cyclophosphamide) and additional intravenous steroids.

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At his November 2006 visit, he complained of "cognitive issues at work. Forgetful. Loses train of thought," although his reading had improved somewhat. Notably on that visit, he was started on Provigil for energy and Aricept and Namenda for his cognitive dysfunction.

In 2007, his symptoms continued to fluctuate. He continued to complain of cognitive dysfunction, which had improved since June of the previous year. He stated in June of 2007 that his "reading is slower, especially for complex material." He had three lesions on his repeat MRI scan. He also described a new symptom of burning in his arms and legs.

In 2008, he continued to complain of cognitive issues. In February, he complained of being in a "fog at work," which he attributed to being in a certain office building. Sometimes he would lose words and his speech would slur.

In April of 2009, he noted that while he was "mentally better," he continued to find it hard to focus mentally and read for long periods of time. He noted ongoing visual loss in his right visual field, more nausea and bitemporal headaches.

In August, he was hospitalized with diverticulitis, which was a complication of monthly chemotherapy and steroid treatments to slow the progression of his multiple sclerosis.

In September, he was started on a new therapy, intravenous immunoglobulin, which did not benefit his condition. He complained at his visit of intermittent chest pains, "foggy" sensations in his head that would start at noon and worsen as the day continued. He described fatigue, inability to focus in his job and his overall limitations in the scope of what he was able to do in his job. He also complained of new visual symptoms and found himself missing stop signs while driving. I recommended that he should apply for disability because I believed that he was in relapse and to re-evaluate his condition and begin additional treatments.

In 2010, I referred him to Dr. Yanina Kostina-O'Neil, a neuro-ophthalmologist affiliated with Yale University School of Medicine, due to his new visual symptoms and continued complaints of reading difficulties. The neuro-opthalmic examination documented that he "has convergence insufficiency, which I believe is the main reason he is having a difficult time reading. His visual field is consistent with right superior homonymous visual field loss. It is perfectly explained by an MS related lesion in the left temporal region." Dr. Kostina-O'Neil believed that he had mild optic neuritis and could have MS related neuropathy.

Since that period, Mr. Wenger has been treated with natalizumab monthly infusions to control his multiple sclerosis. Natalizumab is a second line therapy recommended for patients who are inadequately treated with injectible first line drugs. He has also been treated with escitalopram for his depression and armodafanil for his fatigue in addition to amphetamine salts. While his condition has been relatively stable, there has been no improvement as would be expected.

Neuropsychological Testing

Initial neuropsychological testing was performed in March of 2010. His examiner, Richard Delaney, Ph.D. noted "mild mental slowing that is evident on some tasks of processing and psychomotor speed." On perceptual motor tasks, visual scanning was slowed "mildly when the search task increases in complexity." It was also noted that "Mr. Wenger struggles at time to focus and sustain effective vision. He can usually overcome his difficulty and complete a visual task with increased effort, though his results may be mildly slowed." With respect to speech-language tasks, "Mr. Wenger performed in the borderline on a timed measure of verbal phonemic fluency." Overall, Mr. Wenger scored in the superior range on many of the cognitive scales tested with the exception of processing speed, in which his performance was in the 27th percentile. The 27th percentile with respect to processing speed signifies that Mr. Wenger was not cognitively intact. These abnormalities in his neuropsychological testing, although detected at a later date, were pre-existing impairments in the summer of 2009, and were substantiated in my clinical examination and Mr. Wenger's self report throughout the time that I have cared for him.

These results were confirmed and extended on follow up neuropsychological testing with Amy Palmer, Psy.D. in March of 2011. More information was provided in terms of his cognitive difficulties at work. Mental processing speed was in the Low Average Range. Also, falling into the Low Average Range was the percentage of information retained between the Immediate and Delayed Memory Indices and the accuracy of the information was in the Low Average Range. He was also "Mildly Impaired" when asked to recall as a second word list after learning an initial word list. He also demonstrated difficulty with "impulse control and attention. Again, this is thought to represent a decline." While, it was noted that Mr. Wenger was clinically depressed during both neuropsychological tests but this was not felt to influence his testing on cognitive measures: "Psychiatrically, Mr. Wenger is clinically depressed. However, research has shown that depressed individuals who produce good effort on testing, as Mr. Wenger did, do not display cognitive impairment secondary to depression. Therefore, his cognitive impairments are extremely likely to be due to his Multiple Sclerosis." His examiner, Dr. Palmer concluded: "Based on Mr. Wenger's job description, I do not believe that he would be able to function at acceptable levels given his cognitive impairments. His job requires ability to multitask, pay attention, remember more than one data set at a time and think and speak quickly. Unfortunately, these areas have been compromised for Mr. Wenger."

Reviews by the Insurer

The insurer had reviews completed by its own consultants. I would like to comment on the reviews completed by James R. Boone, Ph.D. and Leonid Topper, MD.

In the Neuropsychological Review by Dr. Boone on July 9, 2011, several assertions were made that were extrapolations from the results of the neuropsychological tests that directly contradict the conclusions of Drs. Delaney and Palmer, e.g., "In this reviewer's

opinion, Mr. Wenger's few mild performance difficulties are unlikely to result in functional impairment, particularly for an individual who has reportedly been successfully working with MS symptoms since 2006." There is ample evidence that Mr. Wenger was not able to successfully perform at a level required for his position, which required significant technological expertise and the ability to assimilate new technology skills quickly in a rapidly changing field and to interact with other senior executives in the company. Furthermore, as the record shows, in an effort to stabilize his condition he was treated with a number of both FDA-approved and off-label treatments, including Rebif, Copaxone, cyclophophosphamide, methylprednisolone, plasma exchange, IVIG and, now, Tysabri. The variety and number of treatments attest to the complexity of treating and trying to improve Mr. Wenger's function. In addition, he was treated with drugs to try and improve his cognition, including stimulants such as amphetamine salts, Nuvigil, Provigil, Concerta and Vivance and drugs to improve memory such as Aricept and Namenda. Dr. Boone further notes that, "Although Multiple Sclerosis with MRI abnormalities can certainly be associated with cognitive impairment, this reviewer notes that cognitive impairment is not automatically presumed." This statement ignores Mr. Wenger's report of cognitive impairment, his inability to successfully perform in his job after June of 2006, his results on his neuropsychological testing and the fact that the location of his lesion on MRI in the left thalamus, involving both grey and white matter, produces the type of deficits that have been observed. I would argue that the involvement of grey matter, e.g., nerve cell bodies, as well as white matter, e.g., axons, produced a stroke-like clinical picture. There are no inconsistencies in Mr. Wenger's self report, clinical findings or objective findings. The reviewer is highly presumptuous in reinterpreting the results and conclusion of two experienced neuropsychologists who performed the testing.

The Neurology Medical Reviews by Dr. Topper on June 3, 2011 and July 11, 2011, documents a number of functional limitations, both cognitive and physical in his summary (e.g. limited to 4 hours of computer use and reading in an 8-hour day, limited to 1-hour at a time; limited to 4 hours of complex cognitive tasks in an 8-hour day, limited to 1-hour at a time.). The statement by Dr. Topper that "Based on the medical records and considering the corrected date of neuropsychological evaluation, there is no clinical evidence of any significant change in claimant's work capacity around 09/25/2009. Previously this date was considered a believable date of change considering that neurocognitive profile was normal prior to this date and became abnormal after this date." In other words, Dr. Topper states that the complex cognitive task 4-hour limitation should not apply prior to the March 8, 2011 neuropsychological evaluation. But, there is abundant evidence that Mr. Wenger's neurocognitive profile was not normal as early as 2006 and certainly by 2009. I believe that he had a fixed/irreversible deficit from his left thalamic lesion that did not improve after his initial presentation. This impacted his ability to perform his job duties despite his considerable effort to compensate for his cognitive dysfunction and fatigue and willingness to consider any and all treatments that might help his condition.

Although Dr. Topper was board certified in neurology whether he was an MS specialist or had any experience in treating patients with multiple sclerosis is not listed, and

unlikely based on his assessment. It is well known, for instance, that clinical attacks can occur in the absence of new or active MRI lesions given the limited sensitivity of the test; therefore, the absence of the latter is by no means indicative of clinical stability. The FDA considers MRI to be an ancillary test of disease activity, not a replacement for a clinical evaluation. Furthermore, Dr. Topper notes that the there was no documentation "at the level of Mini Mental Status Examination." The Mini Mental Status Examination is a very crude measure of cognition (2) and by no means reflects difficulties in higher level cognitive function (see Appendix).

Similarly, the EDSS is not and was never intended to serve as a scale for employment related disability. It's primary use is to assess neurological changes for the purpose of natural history studies and clinical trials of multiple sclerosis therapeutics. It is an ordinal scale that is heavily weighted to ambulation ability. It under weighs fatigue and cognitive impairments, which are the main causes of work related disability. In Mr. Wenger's situation, his EDSS scores in the 2.0 to 4.0 range reflect the fact that, although he has mild to moderate physical impairment, he is able to walk without the use of a cane, crutch or brace. These issues are unrelated to his reasons for his being unable to work. By contrast, I have cared for many individuals with EDSS scores in the 6 to 8 range without cognitive deficits who are able to continue their white collar jobs and even run businesses despite the fact that they are dependent upon assistive devices for ambulation or are nonambulatory.

Conclusion

It is my opinion that Mr. Wenger's cognitive and physical impairments due to multiple sclerosis are substantiated by his MRI scans demonstrating lesions, results of his neuropsychological testing, and his reports of specific cognitive problems at work. These impairments are consistent with his inability to work at both his former position with NASDAQ as well as any other occupational position suitable to his training and experience as of September 25, 2009. Mr. Wenger's primary multiple sclerosis lesion was in the left thalamus on the dominant side of the brain. The thalamus is involved in both language and cognition as well as behavioral and mood changes, as studies of patients with unilateral and bilateral thalamic lesions, have shown (1,2). Mr. Wenger never returned to his baseline cognitive function after his initial attack of MS, a fact which the medical record clearly documents. Despite this, he made a substantial effort to remain working and tended to minimize his difficulties. He recalls, however, that he was not able to keep up with the cognitive demands of his work (e.g. unable to put a presentation together after a week of working on it; difficulty passing a course on JAVA, a programming language, which in the past would have come quite easily to him). The abnormalities in his neuropsychological testing, although detected at a later date, were pre-existing impairments in the summer of 2009, and were substantiated in my clinical examination and Mr. Wenger's self report throughout the time that I have cared for him. Furthermore, his visual impairments were significant and added to his difficulty in performing his work-related duties.

As a specialist in Multiple Sclerosis for the past twenty years, I have evaluated and treated patients similar to Mr. Wenger, e.g., previously high functioning individuals whose cognitive dysfunction is affected out of proportion to any obvious physical disability and are unable to continue to work, several in computer-related fields. Studies have shown that more than 50 percent of individuals with multiple sclerosis are unemployed (4,5). One of the major associations with unemployment in several studies are cognitive dysfunction and fatigue (3). With his cognitive dysfunction, fatigue, pain and visual problems, Mr. Wenger would clearly be a rare exception if he were able to function normally in his occupation as a technology manager and or any other occupation for which he may otherwise be suited.

Sincerely,

Joseph B. Guarnaccia, M.D

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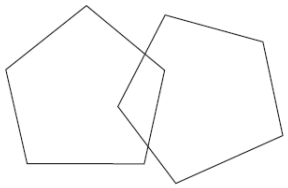
STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

	QUESTION	TIME ALLOWED	SCORE
1	a. ***What year is this?***	10 seconds	/1
	b. ***Which season is this?***	10 seconds	/1
	c. ***What month is this?***	10 seconds	/1
	d. ***What is today's date?***	10 seconds	/1
	e. ***What day of the week is this?***	10 seconds	/1
2	a. ***What country are we in?***	10 seconds	/1
	b. ***What province are we in?***	10 seconds	/1
	c. ***What city/town are we in?***	10 seconds	/1
	d. ***IN HOME – What is the street address of this house?*** ***IN FACILITY – What is the name of this building?***	10 seconds	/1
	e. ***IN HOME – What room are we in? IN FACILITY – What floor are we on?***	10 seconds	/1
3	**SAY:** ***I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.*** Say the following words slowly at 1-second intervals **- ball/ car/ man**	20 seconds	/3
4	***Spell the word WORLD. Now spell it backwards.***	30 seconds	/5
5	***Now what were the three objects I asked you to remember?***	10 seconds	/3
6	**SHOW** wristwatch. **ASK:** ***What is this called?***	10 seconds	/1
7	**SHOW** pencil. **ASK**: ***What is this called?***	10 seconds	/1
8	**SAY:** ***I would like you to repeat this phrase after me: No ifs, ands or buts.***	10 seconds	/1
9	**SAY:** ***Read the words on the page and then do what it says.*** Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/1
10	**HAND** the person a pencil and paper. **SAY:** ***Write any complete sentence on that piece of paper.*** (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11	**PLACE** design, eraser and pencil in front of the person. **SAY**: ***Copy this design please.***  Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/1
12	**ASK** the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. **SAY**: ***Take this paper in your right/left hand*** (whichever is non-dominant), ***fold the paper in half once with both hands and put the paper down on the floor*** . Score 1 point for each instruction executed correctly. Takes paper correctly in hand Folds it in half Puts it on the floor	30 seconds	/1 /1 /1
	TOTAL TEST SCORE		**/30**

Note: This tool is provided for use in British Columbia with permission by Dr. William Molloy. This questionnaire should not be further modified or reproduced without the written consent of Dr. D. William Molloy.

GLOBAL DETERIORATION SCALE (GDS)

Stage	Deficits in cognition and function	Usual care setting
1	**Subjectively and objectively normal**	Independent
2	• Subjective complaints of mild memory loss. • Objectively normal on testing. • No functional deficit	Independent
3	**Mild Cognitive Impairment (MCI)** • Earliest clear-cut deficits. • Functionally normal but co-workers may be aware of declining work performance. • Objective deficits on testing. • Denial may appear.	Independent
4	**Early dementia** • Clear-cut deficits on careful clinical interview. Difficulty performing complex tasks, e.g. handling finances, travelling. • Denial is common. Withdrawal from challenging situations.	Might live independently – perhaps with assistance from family or caregivers.
5	**Moderate dementia** • Can no longer survive without some assistance. • Unable to recall major relevant aspects of their current lives, e.g. an address or telephone number of many years, names of grandchildren, etc. Some disorientation to date, day of week, season, or to place. They require no assistance with toileting, eating, or dressing but may need help choosing appropriate clothing.	At home with live-in family member. In seniors' residence with home support. Possibly in facility care, especially if behavioural problems or comorbid physical disabilities.
6	**Moderately severe dementia** • May occasionally forget name of spouse. • Largely unaware of recent experiences and events in their lives. • Will require assistance with basic ADLs. May be incontinent of urine. • Behavioural and psychological symptoms of dementia (BPSD) are common, e.g., delusions, repetitive behaviours, agitation.	Most often in Complex Care facility.
7	**Severe dementia** • Verbal abilities will be lost over the course of this stage. • Incontinent. Needs assistance with feeding. • Loses ability to walk.	Complex Care

Adapted by Dr. Doug Drummond from Reisberg B, Ferris SH, Leon MJ, et al. The global deterioration scale for assessment of primary degenerative dementia. American Journal of Psychiatry 1982;139:1136-1139.

Neurology®

The thalamus and multiple sclerosis: Modern views on pathologic, imaging, and clinical aspects

Alireza Minagar, Michael H. Barnett, Ralph H.B. Benedict, et al.

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The thalamus and multiple sclerosis

Modern views on pathologic, imaging, and clinical aspects

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ABSTRACT

The paired thalamic nuclei are gray matter (GM) structures on both sides of the third ventricle that play major roles in cortical activation, relaying sensory information to the higher cortical centers that influence cognition. Multiple sclerosis (MS) is an immune-mediated disease of the human CNS that affects both the white matter (WM) and GM. A number of clinical observations as well as recent neuropathologic and neuroimaging studies have clearly demonstrated extensive involvement of the thalamus, basal ganglia, and neocortex in patients with MS. Modern MRI techniques permit visualization of GM lesions and measurement of atrophy. These contemporary methods have fundamentally altered our understanding of the pathophysiologic nature of MS. Evidence confirms the contention that GM injury can be detected in the earliest phases of MS, and that iron deposition and atrophy of deep gray nuclei are closely related to the magnitude of inflammation. Extensive involvement of GM, and particularly of the thalamus, is associated with a wide range of clinical manifestations including cognitive decline, motor deficits, fatigue, painful syndromes, and ocular motility disturbances in patients with MS. In this review, we characterize the neuropathologic, neuroimaging, and clinical features of thalamic involvement in MS. Further, we underscore the contention that neuropathologic and neuroimaging correlative investigations of thalamic derangements in MS may elucidate not heretofore considered pathobiological underpinnings germane to understanding the ontogeny, magnitude, and progression of the disease process. *Neurology*® 2013;80:210–219

GLOSSARY

CIS = clinically isolated inflammatory demyelinating syndrome; **DIR** = double inversion recovery; **DTI** = diffusion tensor imaging; **EDSS** = Expanded Disability Status Scale; **GM** = gray matter; **LGN** = lateral geniculate nucleus; **MS** = multiple sclerosis; **NAGM** = normal-appearing gray matter; **NAWM** = normal-appearing white matter; **SWI** = susceptibility-weighted imaging; **WM** = white matter.

Multiple sclerosis (MS) is a progressive inflammatory and degenerative disease of the human CNS that leads to demyelination and neuronal/axonal loss. Both the etiology and cure for MS remain elusive, and for many years scientific research into the pathogenesis of MS has heavily focused on a disease principally affecting CNS white matter (WM).

Notwithstanding the traditional focus upon WM as the predominant target of the disease mechanisms in MS, recent findings, which indicate significant gray matter (GM) involvement, are an important and substantial refinement in our understanding of the pathobiological underpinnings of the disease process in MS, of particular relevance to cognitive decline as well as overall disease worsening.[1,2] Neuropathologic data implicate significant cortical demyelination and neuro-axonal and synaptic loss in both the early and late phases of the disease process.[2–5] Both cortical[3] and subcortical demyelination are observed during the course of MS, targeting a landscape of GM-rich structures including the thalamus, hippocampus, caudate, putamen, globus pallidus, and other structures of the basal ganglia.[5,6]

Both postmortem and in vivo studies have revealed extensive MS lesions of the GM structures.[1,7,8] In general, the neuropathologic features of GM involvement in MS differ significantly

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

from WM lesions.[5] For example, certain features such as lymphocyte infiltration, complement deposition, and disruption of the blood–brain barrier are typically not detected in the GM of chronic autopsy samples but have been reported in cortical lesions of active MS. More robust and long-lasting neuroinflammation is the dominant component of newly forming WM lesions. Similar to diffuse involvement of the WM in MS, demyelination of the cerebral cortex and cerebellum,[1] deep GM structures,[8,9] and the GM of the spinal cord[10] have been reported, supporting the concept of "diffuse brain involvement" in MS. Pathology within the thalamus is frequently observed in MS, but less well characterized when compared to the delineation of WM compartment lesions.[7,8] As a major portion of the diencephalon in primates, the thalamus serves as a gateway to the cerebral cortex and is heavily involved with its activity. However, its unique structural division into various nuclear complexes enables the thalamus to connect with other subcortical structures. Neuroanatomically, as a "relay organ," the thalamus is involved in a wide range of neurologic functions including motor, sensory, integrative, and higher cortical functions. Further, the thalamus also plays a significant role in other functions such as the regulation of sleep and wakefulness, memory, emotion, consciousness, awareness, and attention. The thalamus is also involved in ocular motility, posture, and executive function. Location, unique functions, and vulnerability to MS neuropathology from the earliest disease stages[11–14] render the thalamus a critical barometer of diffuse neuropathologic damage in MS. Advanced neuropathologic and neuroimaging methods are slowly emerging, providing us with a better view of the full extent of thalamic abnormalities in patients with MS.

Thalamic axons are well known to transmit information between a number of subcortical and specific cortical areas. As such, damage to the thalamic nuclei and their connections potentially impairs a wide range of neurologic functions that may clinically translate into significant cognitive and mental disability.[15,16] Thalamic pathology in MS accumulates on a background of normal age-related reduction in thalamic volume,[17] which is in itself associated with a decline in cognitive capacity, particularly mental speed and information processing speed.[18] Predicated on the known role of the thalamus in the normal operation of the human CNS, and based on the growing knowledge of the extent of its damage and involvement in the pathogenesis of MS, we aimed to review and discuss these abnormalities in the context of recently emerging neuropathologic and neuroimaging studies.

THALAMIC NEUROPATHOLOGY IN MS The notion that clinically relevant MS pathology is restricted to focal WM lesions has been overwhelmingly negated by an expanding body of neuropathologic data implicating significant cortical myelin, neuro-axonal, and synaptic loss[2–5,9,19] in both early and late stages of the disease. Pathology afflicting the deep GM structures, in particular the thalamus, is frequently observed in MS, but less well studied. Significant neuropathologic and neuroimaging studies addressing thalamic involvement in MS are presented in the table. While informative, these studies are limited by their small sample size, retrospective design, registration biases, and an absence of treatment effects on thalamic MRI-related outcomes over the course of time.

Distribution. The extent of subcortical GM demyelination correlates well with the extent of cortical, but not WM, demyelination,[8] although more studies are needed to determine the relationship between the pathologic processes operating in the subcortical GM with respect to those in the WM. Thalamic GM lesions may extend into the surrounding WM; however, a significant proportion of deep gray plaques are in fact confined to the subcortical GM, with edges that are abruptly demarcated in juxtaposition with well-recognized anatomic WM borders.[8,10] Extensive, confluent subependymal GM demyelination is relatively common in the paraventricular nuclei of the thalamus,[10] raising the possibility of a pathogenic factor within the CSF. While this hypothesis is supported by the demonstration of B-cell aggregates in association with the fourth ventricle and its lateral recesses in the experimental allergic encephalomyelitis model of MS,[20] the "follicles" identified in the meninges in topographic association with zones of subpial demyelination in the cortex of some patients with secondary progressive disease[21] have not been identified in association with the ventricular system in humans.

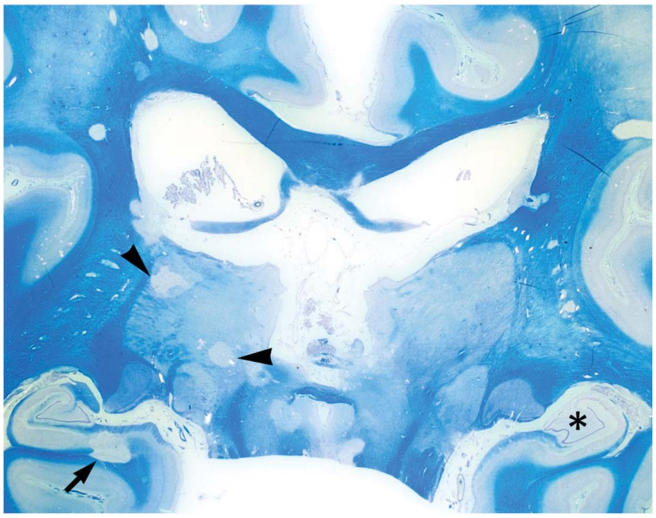
Diffuse microglial activation is detectable in thalamic normal-appearing GM (NAGM),[8] but to a lesser degree than one typically observes in the normal-appearing WM (NAWM) of patients with long-standing disease. Extralesional microglial activation, characterized by thickening of cell processes and upregulation of human leukocyte antigen–DR expression, is a highly sensitive, albeit nonspecific, indicator of CNS pathology. In MS, retrograde and anterograde diffuse axonal injury is the

Table Summary of the most relevant articles on the neuropathologic and neuroimaging findings of thalamic involvement in multiple sclerosis

Original article	No. of subjects and disease subtype	Major neuropathologic and neuroimaging findings
Cifelli et al. (2002)[7]	14 SPMS and 14 controls	Utilizing MRI, MRS, and postmortem histopathologic studies with focus on thalamic neuronal loss, the authors reported significant neuronal damage in MS.
Wylezinska et al. (2003)[51]	14 RRMS and 14 controls	Utilizing structural MRI and MRS studies, the authors assessed thalamic neurodegeneration in patients with RRMS and reported reduction of both NAA concentration and thalamic volume, which indicated a neurodegeneration component in the neuropathology of MS. The authors concluded that the decrease in NAA concentration and thalamic volume suggests that neurodegeneration contributes to the neuropathology of MS in an even earlier stage of the disease.
Vercellino et al. (2005)[9]	6 MS (3 RRMS and 3 SPMS)	The authors performed a neuropathologic examination of MS brains to assess the extent and distribution of GM demyelinating lesions in MS with a focus on neuronal loss and synaptic loss. They reported the presence of demyelinating lesions in the thalamus, cerebral cortex, basal ganglia, and hippocampus. It was concluded that GM demyelination and neuronal loss could contribute to disability and cognitive decline in MS.
Davies et al. (2004)[47]	38 RRMS and 35 controls	Utilizing MTR in patients with early RRMS, the authors reported abnormality of thalamic MTR and thalamic involvement within the first 5 years of MS onset.
Houtchens et al. (2007)[16]	79 MS (62 RRMS, 16 SPMS, and 1 PPMS) and 16 controls	Normalized thalamic volume was lower in patients with MS compared to controls, and cognitive performance in all domains was related to thalamic volume in the MS group. A weak correlation between thalamic atrophy and physical disability score was detected. However, cognitive performance in all domains was moderately to strongly related to thalamic volume in patients with MS. The authors concluded that thalamic atrophy was a clinically relevant biomarker of the neurodegenerative disease process in MS.
Mesaros et al. (2008)[37]	28 pediatric RRMS and 21 controls	In pediatric patients with MS, different from what occurs in adult patients with MS, GM atrophy appears to affect the thalamus exclusively.
Vercellino et al. (2009)[8]	14 MS (7 SPMS, 6 RRMS, and 1 hyperacute MS) and 12 controls (6 normal and 6 with ALS)	Demyelination and neurodegenerative changes are common in MS deep GM and may contribute to clinical deficits.
Ramasamy et al. (2009)[13]	71 MS (40 RRMS, 17 PPMS, and 14 SPMS), 17 CIS, and 38 controls	This study supported selective deep GM atrophy (mostly thalamic), showed cerebellar WM atrophy from the earliest clinical stages, and showed that cortical thinning advances with disease progression.
Gilmore et al. (2009)[10]	14 MS (11 SPMS, 2 PPMS, and 1 RRMS) and 3 controls	The authors reported the presence of significant regional variations in the extent and pattern of GM demyelination in MS.
Henry et al. (2009)[11]	24 CIS and 18 controls	A stepwise regression analysis demonstrated that thalamocortical lesion volume and the mean diffusivity in track regions connecting lesion and thalami were significantly correlated with thalamic volumes in patients, explaining 66% of the variance, a finding not observed in regions outside the thalamocortical WM.
Tovar-Moll et al. (2009)[49]	24 MS (13 RRMS and 11 SPMS) and 24 controls	Utilizing DTI at 3 T, the authors assessed thalamic involvement and its impact on clinical disability in patients with MS. They concluded that DTI was able to detect abnormalities in the normal-appearing thalamus of patients with MS and there was an association between thalamic DTI measures and functional impairment in MS.
Rocca et al. (2010)[15]	73 relapse-onset MS (20 CIS, 34 RRMS, and 19 SPMS) and 13 controls	Utilizing conventional imaging and MTR, the authors detected that thalamic atrophy was correlated with accumulation of disability in patients with MS. In addition, WM lesions were likely to contribute to the thalamic tissue loss observed in patients with MS.
Audoin et al. (2010)[33]	62 CIS and 37 controls	Based on this study which involved patients with CIS, atrophy mainly affected the limbic system and the deep GM (bilateral thalami) at the first stage of MS.
Calabrese et al. (2011)[14]	105 CIS and 24 controls	The study found that selective GM atrophy is relevant in patients with CIS who convert early to MS. The multivariate analysis identified the atrophy of the superior frontal gyrus, thalamus, and cerebellum as independent predictors of conversion to MS.
Mesaros et al. (2011)[48]	54 PPMS and 8 controls	Using conventional and DTI brain scans, the authors assessed thalamic damage in patients with PPMS and concluded that thalamic damage predicts the evolution of PPMS.
Hagemeier et al. (2012)[41]	42 CIS and 65 controls	Patients with CIS showed significantly increased content and volume of iron, as determined by abnormal SWI-phase measurement in the various SDGM structures, especially in the pulvinar nucleus of thalamus, suggesting that iron deposition may precede structure-specific atrophy.
Batista et al. (2012)[59]	86 MS (59 RRMS and 27 SPMS) and 25 controls	Utilizing 3 T brain MRI, the authors demonstrated that the basal ganglia, thalamus, and neocortical atrophy predict slowed cognitive processing in MS.
Zivadinov et al. (2012)[44]	233 MS (169 RRMS and 4 SPMS) and 126 controls	Utilizing SWI-filtered phase images, the authors assessed subcortical GM structure in patients with MS compared to control subjects, and reported abnormal phase in patients with MS in a number of GM regions, especially in the pulvinar nucleus of thalamus, indicative of higher iron content in patients with MS, which was related to more severe lesion burden and brain atrophy.

Abbreviations: ALS = amyotrophic lateral sclerosis; CIS = clinically isolated syndrome; DTI = diffusion tensor imaging; GM = gray matter; MRS = magnetic resonance spectroscopy; MS = multiple sclerosis; MTR = magnetization transfer ratio; NAA = *N*-acetylaspartate; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SDGM = subcortical deep gray matter; SPMS = secondary progressive multiple sclerosis; SWI = susceptibility-weighted imaging; WM = white matter.

Figure 1 Coronal section through the posterior thalamus, secondary progressive multiple sclerosis

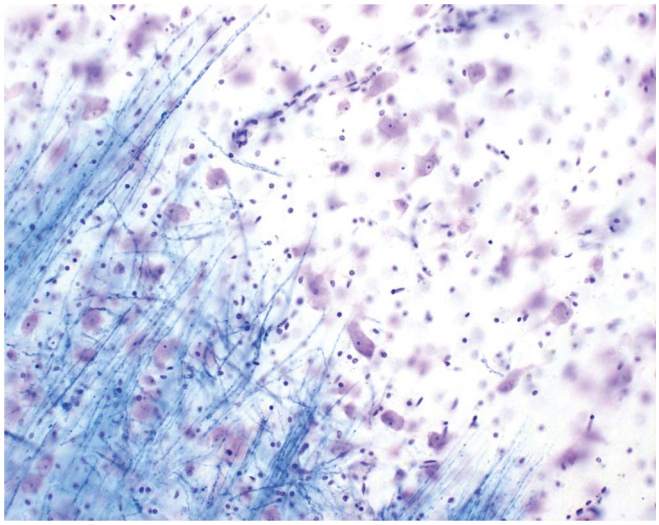


Focal chronic lesions are present in the right pulvinar nuclei and the lateral posterior nucleus of the thalamus (arrowheads), the latter with a remyelinating fringe. Demyelination is also present in the deep gray matter of the right caudate nucleus in association with an adjacent chronic white matter lesion. Additionally, there is a leukocortical lesion in the subiculum of the right hippocampal formation (arrow), diffuse demyelination of the left hippocampus proper (asterisk), and involvement of the periaqueductal gray matter. Classic small focal white matter lesions are present in the white matter, including the corpus callosum. Luxol fast blue.

likely substrate underlying this finding in both NAWM and NAGM, although diffusion of soluble cytokines from nearby focal lesions, or a primary innate immune response, are possible contributors.

Pathology of focal lesions. Histopathologic characterization of the thalamic lesions (figure 1) recapitulates the spectrum of active, chronically demyelinated, and remyelinated pathologies observed in the WM. Chronic lesions, completely devoid of myelin (figure 2), predominate in the few existing pathologic descriptions, and exhibit a relatively subdued astrocyte reaction as indicated by glial fibrillary acid protein immunohistochemistry.[8] Within rare active lesions, the intensity of the macrophage infiltrate mirrors myelin density and therefore varies according to location within the thalamus. Similar to changes demonstrated in cortical GM lesions of autopsy cases,[22–24] both adaptive (T and B cell perivascular and parenchymal infiltration) and innate (microglial activation/macrophage infiltration) inflammation in the thalamus is constrained when compared with classic active WM lesions,[8] a factor that potentially limits neuroaxonal injury in evolving lesions. However, this view has been recently challenged by Lucchinetti et al.,[3] who demonstrate significant cortical GM inflammation in biopsy cases of early MS. Sampling bias in both early biopsy and end-stage autopsy studies may explain these discrepant findings; larger neuropathologic studies of the subcortical GM structures are required in order to corroborate or refute these observations.

Figure 2 Border zone of a chronic thalamic lesion, secondary progressive multiple sclerosis



The gray matter lesion (top right) is devoid of myelin (stained blue) and hypocellular. Comparison with adjacent normal-appearing gray matter (bottom left) discloses a reduction in the number of neurons and a paucity of cells with oligodendrocyte morphology (Luxol fast blue).

Neuronal pathology. Thalamic pathology in MS cannot be viewed in isolation. As a discrete, symmetric brain structure with widespread cortical and subcortical connections, the thalamus provides the ideal neuropathologic (and MRI) substrate for examining neurodegeneration in MS. Cifelli et al.[7] examined the thalami of 10 patients with MS (9 progressive, 1 relapsing) and demonstrated a reduction in both thalamic volume (21%) and nonlesional neuronal density (22%) vs age- and gender-matched controls, confirming their in vivo MRI observations in a separate cohort of patients with secondary progressive MS. A similar degree of neuronal loss was subsequently described in nonlesional mediodorsal thalamic nucleus,[8] raising the possibility that neuronal loss is a retrograde event consequent to axonal transection in WM tracts projecting from the thalamus, or secondary to transsynaptic deafferentation of thalamic neurons. Altered neuronal morphology has also been described in the lateral geniculate nucleus (LGN) of the thalamus,[25] which receives projections from axons in the optic tract. The authors describe significant variation and an overall reduction in neuronal size in the parvocellular, but not magnocellular, layers of the LGN, which they attribute to retrograde damage resulting from differential susceptibility of small diameter axons (in the optic tract) to MS-related injury. It seems unlikely that Wallerian or transsynaptic degeneration is the sole cause of neuronal damage in the thalamus. Direct injury from diffusable cytokines, oxidative stress, excitotoxicity, and CD8 T-cell–mediated cytotoxicity are all contenders, particularly in cases with identifiable focal inflammatory lesions. Alteration in neuronal

morphology and size within demyelinated thalamic GM lesions compared with adjacent nonlesional GM supports this hypothesis.[8] Finally, surviving neurons within subcortical GM lesions invariably shed their satellite oligodendrocytes, potentially diminishing trophic support and disrupting the perineuronal microenvironment. In particular, perineuronal glutamate homeostasis may be dysregulated by the loss of glutamate transporter–expressing satellite oligodendrocytes.[24]

NEUROIMAGING CHARACTERISTICS OF THALAMIC INVOLVEMENT IN MS Due to inherent structural differences between GM and WM and as a result of differences in inflammation characteristics, cortical GM lesions seem to maintain a normal water proton concentration and, unlike WM lesions, are not typically detectable as T2 hyperintense foci on MRI.[26] However, thalamic lesions are usually more visible than cortical lesions, likely because the thalamus is normally more densely myelinated. The introduction of double inversion recovery (DIR) in the study of MS may play an important step in refining the conspicuity of GM lesions.[6] By suppressing the signal from normal WM and CSF, DIR sequences provide excellent differentiation between GM and WM.[27] In a series of recently published studies from the Amsterdam (Netherlands)[6] and Padova (Italy)[28] groups, DIR imaging most frequently identified cortical lesions in male patients, progressive MS, and in those with CSF IgG oligoclonal bands. However, it is now evident that DIR imaging detects only a fraction of the real burden of cortical GM pathology that is present in patients with MS, with an average sensitivity of only 18%.[29] Therefore, although pathologically validated DIR scoring indicates a high specificity for the detection of GM lesions, the sensitivity is very low, with a false-positive rate of at least 10%.[29,30] The value of DIR in the detection of lesions in subcortical GM lesions was not investigated.

Contemporary investigations have focused on determining the extent of cortical and subcortical GM pathology in patients presenting with a first clinically isolated inflammatory demyelinating syndrome (CIS),[11–13,31–33] or following conversion to clinically definite MS.[14,34] It has been reported that global and cortical GM volume measures are not sensitive enough to detect GM atrophy at the time of the initial attack.[31] Therefore, GM atrophy studies in patients with CIS have increasingly turned to regional segmentation techniques to identify specific structures with a stronger predilection for disease susceptibility and conversion to clinically definite MS. A number of independent studies have shown that loss of volume in the thalamus is one of the earliest and most prominent signs of subcortical GM pathology when patients present with CIS.[11–14,31,33,35] Progressive atrophy of the thalamus (figure 3) has been shown in all different MS disease types[12,13,15,36,37] and thalamic volume loss has also been detected in pediatric patients with MS.[37–40]

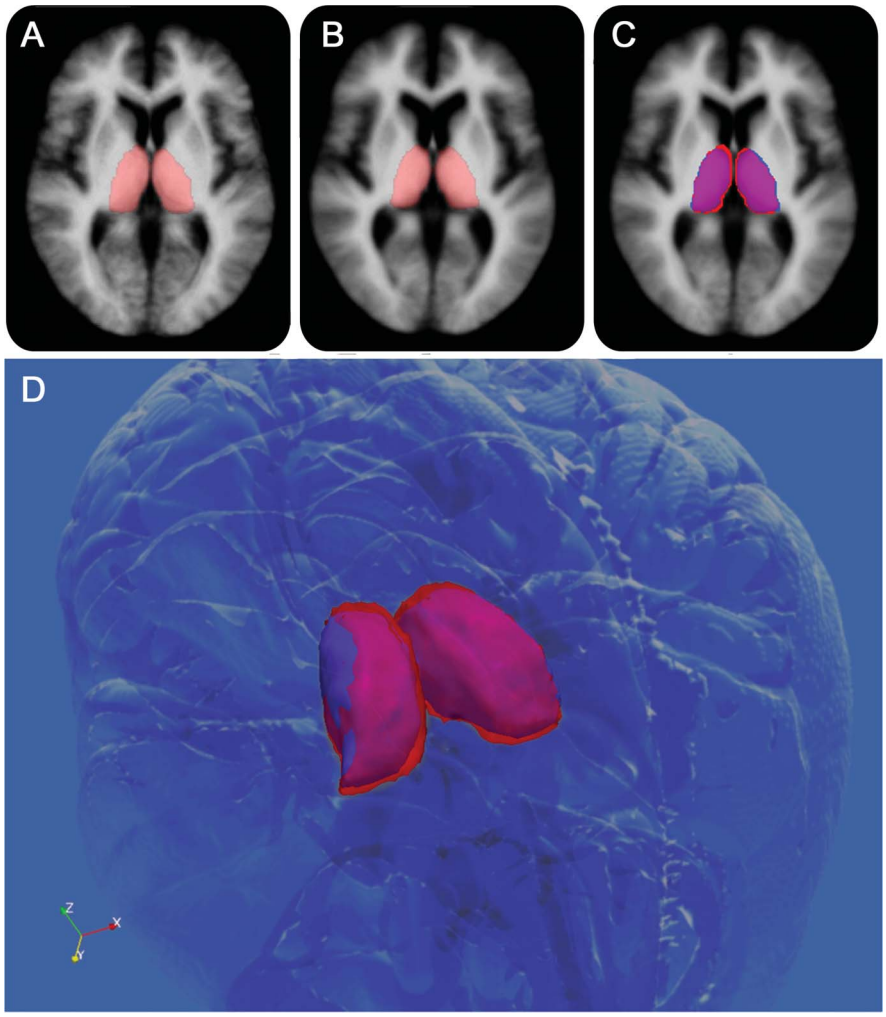
In a recent study of 42 patients with CIS, it was demonstrated that deposition of iron, as estimated by susceptibility-weighted imaging (SWI), in the thalamus and the pulvinar nucleus of the thalamus may precede the development of structure-specific thalamic atrophy at MS clinical onset.[41] This finding has to be confirmed in future studies; however, it is in keeping with mounting evidence derived from T2 hypointensity,[42,43] SWI,[44] and relaxometry[45] studies that showed that iron overload is dominant in the thalamus of patients with MS. One can hypothesize that a vicious cycle involving proinflammatory cells, atrophy of the thalamus, and possible iron accumulation may occur throughout the course of MS. Characterizing the temporal and dynamic interplay of these potential pathobiologic mechanisms from the first clinical onset mandates further investigation; however, at this time there is no definitive answer for the role of iron in relation to thalamic damage in patients with MS.

A number of diffusion-weighted or tensor,[11,46] magnetization transfer,[46–49] and magnetic resonance spectroscopy[7,50,51] imaging studies have investigated the extent of thalamic damage in patients with MS with various disease types (table). All suggested that there may be a common mechanism for WM axonal loss and thalamic neuronal injury related to thalamocortical pathways. One study of 24 patients with CIS sought to determine whether the association between WM lesions and thalamic atrophy at first clinical onset is related to connectivity of these fibers.[11] Diffusion tensor imaging (DTI) fiber tracking was used to create probabilistic templates of thalamocortical WM projections (figure 4A), and to define lesional thalamocortical WM tracks (figure 4B). There was a 10-fold higher density of lesions in thalamocortical projections compared to other brain WM regions. Using a stepwise linear regression model, DTI metrics within lesional thalamocortical tracks and thalamocortical lesion volume accounted for 66% of the variance in thalamic volume, while none of the MRI metrics outside thalamocortical regions contributed to thalamic volume. The authors suggested that focal MS lesions could cause distal WM injury and such damage could, at least in part, lead directly to thalamic neuronal and volume loss.

Taken together, these studies suggest that there is an urgent need for future longitudinal studies investigating the relationship between WM lesion accumulation, thalamic iron deposition, atrophy development, and microstructural alterations using nonconventional MRI metrics from the earliest clinical onset.

CLINICAL MANIFESTATIONS Clinically, thalamic involvement in MS manifests with a spectrum of diverse abnormalities, which range from fatigue and movement disorders to painful syndromes and cognitive decline.

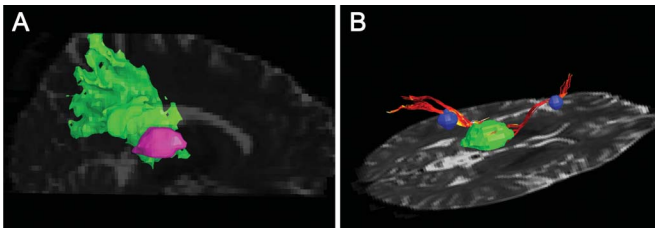
Figure 3 Comparison of thalamic segmentations



Comparison of thalamic segmentations between 26 healthy controls (HC) (age- and sex-matched) (A) and 98 patients with relapsing-remitting multiple sclerosis (MS) (B). (C) Voxel-wise differences between the groups, with magenta representing common areas, red HC-only areas, and blue MS-only areas. Individual patient images were coregistered into the Montreal Neurological Institute 152 space for visualization. A 3D view (D) shows that the MS thalami are smaller overall and slightly shifted away from the midline (most likely by global atrophic processes).

Fatigue is perhaps the most common and disabling symptom of patients with MS and is defined as an overwhelming feeling of a lack of both mental and physical energy. Up to 80% of patients with MS are affected by fatigue, which interferes with a patient's quality of life.[52] Despite significant effort to elucidate the pathogenic mechanisms of fatigue in patients with MS, our knowledge remains marginal, with many unanswered questions. Neuroimaging studies have significantly contributed to the analysis of the pathogenesis of fatigue in MS[36,53] and have revealed functional abnormalities of neuroanatomic pathways involving frontal cortex, basal ganglia, and thalamus.[36,54]

Figure 4 Representative 3D rendering example of fiber tracking from diffusion tensor imaging and voxel-based morphometry in multiple sclerosis



(A) Example of a probabilistic thalamoparietal template. The Montreal Neurological Institute transformed map is coregistered into the patient space; the thalamoparietal region of interest (ROI) is in green and the thalamus ROI in pink. (B) The figure shows 2 thalamocortical fiber tracks (red) seeded through white matter lesions (blue) connecting the thalamus (green) and the cortex (not shown).

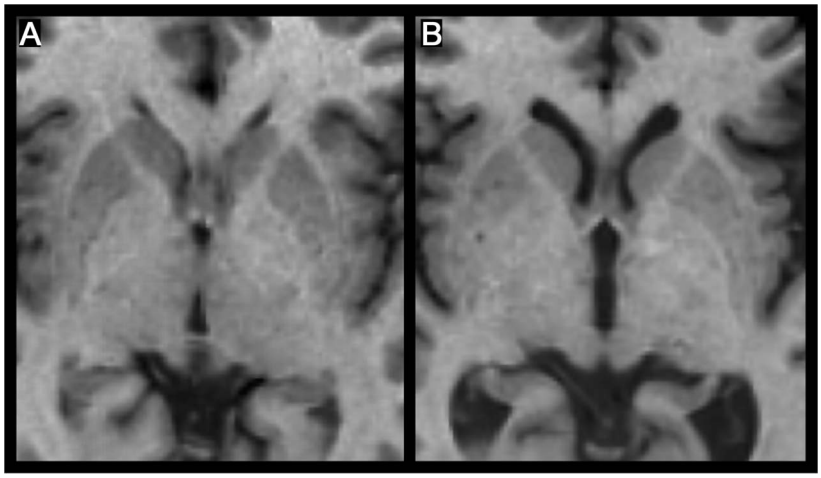
A number of movement disorders have been described in association with MS,[55] which include tremor, parkinsonism, myoclonus, chorea, and paroxysmal dystonia. Paroxysmal dystonia is a painful manifestation of MS that usually presents with unilateral dystonic posture, precipitated by voluntary movement, tactile stimuli, or hyperventilation. Zenzola et al.[56] reported 2 patients with MS with paroxysmal dystonia and thalamic lesions. Both

of these patients had developed demyelinating thalamic lesions contralateral to the paroxysmal symptoms.

Cognitive impairment is perhaps the most devastating and difficult to treat clinical manifestation of thalamic involvement in MS. In 2004, Benedict et al.[57] investigated associations between conventional brain MRI metrics and cognitive function in patients with MS. Contrary to expectation, third ventricle width was most strongly associated with several validated neuropsychological tests. Noting the recent evidence of thalamic atrophy in MS,[7] it was speculated that this finding was driven by atrophy (i.e., ex vacuo dilatation of the third ventricle) of the surrounding thalamic structures (figure 5). The hypothesis was directly investigated by tracing thalami from coronal 3D images, the boundaries being determined with an edge-finding tool and manual adjustment.[16] The raw thalamic volumes were then normalized as a ratio to intracranial volume. Analysis revealed a 16.8% reduction in volume in patients with MS compared to controls. In addition, thalamic fraction was the most significant MRI predictor of consensus standard[58] tests of memory and processing speed. These results were recently replicated in a larger, independent sample using the FIRST technique.[59] A similar theme has recently emerged in the pediatric MS literature. While Mesaros et al.[60] found similar whole brain parenchyma and GM volumes between patients and controls, voxel-based morphometry analysis and statistical parametric mapping detected clusters of reduced GM concentration in the thalamus. Correlations with disease duration and the Expanded Disability Status Scale (EDSS) were not, however, significant. The authors acknowledged that EDSS does not adequately assess cognitive ability. When neuropsychological testing was applied to a pediatric sample,[40] patients with MS again were found to have significantly lower thalamic volume. This time, however, volume loss was the most significant MRI predictor of cognition compared to other MRI metrics. As in the earlier adult literature,[16,57] the degree of correlation was robust, with r values ranging from 0.6 to 0.7. A notable observation from both lines of research is that cognitive dysfunction in multiple spheres has been consistently associated with thalamic atrophy in children and adults with MS. In the pediatric study,[40] the correlation between thalamus volume and IQ was $r = 0.68$. The thalamic fraction or thalamic normalized volume represents a novel approach to quantifying regional GM volume, although it has to be acknowledged that the measure is crude from a neuropsychological perspective. The various nuclei in the thalamus have very different afferent and efferent connections to various brain regions and, as such, mediate disparate functions. Examining correlations with the anterior nucleus, which has rich connections with multiple frontal cortex areas, may shed more light on the link between thalamic pathology and neuropsychological involvement in MS.

DISCUSSION Cortical and subcortical GM involvement is a critically important contributor to the disease process in MS and leads to significant cognitive disability and other potentially devastating neurologic problems in these patients. Thalamic pathology, similar to the cortical pathology, appears to be present in MS from very early on, including at the CIS stage and in pediatric MS. In the progressive phase of MS, which is poorly explained by focal inflammatory WM demyelination, cortical and subcortical GM pathology including

Figure 5 Thalamic atrophy and third ventricle width in multiple sclerosis



Thalamic atrophy is closely related to third ventricle width, as seen in these images of a patient with relapsing-remitting multiple sclerosis (MS) (A) and a patient with secondary progressive MS (B). Both patients have a disease duration of 14 years, and both images are of the same slice in stereotactic Montreal Neurological Institute 152 space.

neuronal and axonal degeneration are the likely substrates for accumulating cognitive and motor dysfunction that characterizes long-standing disease. Further research is needed to elucidate the pathologic processes that lead to MRI-detectable thalamic involvement in the early stages in MS and to characterize its role in disease progression. Existing information about thalamic involvement in MS stems mainly from neuropathologic and neuroimaging studies that have a limited number of subjects and contain no clear practical implications for clinicians. Therefore, larger longitudinal studies are required to assess the validity, accuracy, and sensitivity of these preliminary observations. We also recommend that serial measurement of thalamic volume be utilized as a biomarker in MS clinical trials to assess the patient's response to investigational therapeutic agents.

Finally, future neuropathologic MS studies in conjunction with advanced neuroimaging of GM involvement in general, and the thalamus in particular, should include new imaging techniques such as DIR, volumetric inversion recovery T1-based or phase-sensitive sequences, molecular or metabolite imaging, and high-field and ultrahigh-field MRI to further characterize relevant pathogenic mechanisms associated with disease progression over the short and long term.

AUTHOR CONTRIBUTIONS

Alireza Minagar, Michael H. Barnett, Ralph H.B. Benedict, Daniel Pelletier, Istvan Pirko, Mohamad Ali Sahraian, Elliot Frohman, and Robert Zivadinov substantially contributed to the concept and design of the study. Alireza Minagar, Michael H. Barnett, Ralph H.B. Benedict, and Robert Zivadinov drafted the article, while Daniel Pelletier, Istvan Pirko, Mohamad Ali Sahraian, and Elliott Frohman revised it critically for important intellectual content. All authors had access to the data.

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The thalamus and multiple sclerosis: Modern views on pathologic, imaging, and clinical aspects

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Review

Cognitive, affective and behavioural disturbances following vascular thalamic lesions: A review

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ABSTRACT

During the last decades, many studies have shown that the thalamus is crucially involved in language and cognition. We critically reviewed a study corpus of 465 patients with vascular thalamic lesions published in the literature since 1980. 42 out of 465 (9%) cases with isolated thalamic lesions allowed further neurocognitive analysis.

On the neurolinguistic level, fluent output (=31/33; 93.9%), normal to mild impairment of repetition (=33/35; 94.3%), mild dysarthria (=8/9; 88.9%) and normal to mild impairment of auditory comprehension (=27/34; 79.4%) were most commonly found in the group of patients with left and bilateral thalamic lesions. The taxonomic label of thalamic aphasia applied to the majority of the patients with left thalamic damage (=7/11; 63.6%) and to one patient with bithalamic lesions (=1/1).

On the neuropsychological level, almost 90% of the left thalamic and bithalamic patient group presented with amnestic problems, executive dysfunctions and behaviour and/or mood alterations. In addition, two thirds (2/3) of the patients with bilateral thalamic damage presented with a typical cluster of neurocognitive disturbances consisting of constructional apraxia, anosognosia, desorientation, global intellectual dysfunctioning, amnesia, and executive dysfunctions associated with behaviour and/or mood alterations.

Our study supports the long-standing view of a 'lateralised linguistic thalamus' but restates the issue of a 'lateralised cognitive thalamus'. In addition, critical analysis of the available literature supports the view that aphasia following left or bithalamic damage constitutes a prototypical linguistic syndrome.

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1. Introduction

Functional involvement of the thalamus in cognitive processing was first reported by Hillemand (1925) and Lhermitte (1936) who described atypical aphasic symptoms after a pathologically confirmed left thalamic haemorrhage. These anecdotal descriptions were later confirmed by Fisher (1959) who reported aphasia, next to gnostic and sensory deficits, as one of the main clinical features of left thalamic haemorrhages.

In the sixties, stereotactic surgery, thalamotomies and electric stimulation of the thalamus provided new information about the role of certain thalamic nuclei in cognition. Since then, neurocognitive disturbances such as aphasia, agnosia, amnesia and neglect have been described after thalamic lesions (Fisher, 1959; Bogousslavsky et al., 1986a, 1986b; Schmahmann, 2003).

Since the 1970s, the availability of structural (computerised tomography – CT, magnetic resonance imaging – MRI) and functional (single photon emission computed tomography – SPECT, positron emission tomography – PET, functional magnetic resonance imaging – fMRI) neuroimaging opened a new avenue in the study of neurobehavioural phenomena following thalamic lesions. The inception of these approaches led to a better understanding of the impact of a thalamic lesion on cortical functioning. In addition, the recent development of diffusion tensor imaging (DTI) offers a unique opportunity to study the indirect effects and role of thalamic lesions on cortical dysfunctions due to disconnection of cortical regions underlying language, cognition and behaviour (Hillis, 2008).

Several hypotheses have been advanced to explain the role of the thalamus in higher-order behaviour. In 1997, Nadeau and Crosson described five potential mechanisms associated with lesions of the thalamus: 1) direct impact of the thalamic lesion indicating that the thalamus is a crucial component of the cerebral network underlying neurocognitive processing, 2) disconnection of cortical zones crucially involved in cognition caused by thalamic damage, 3) functional depression of regional neuronal metabolism and cerebral blood flow in anatomically connected cortical regions following dysfunction of the lesioned thalamus. This phenomenon, first described by Von Monakow (1914) is termed 'diaschisis', 4) neuronal deregulation of the cortex and 5) occlusion or stenosis of large cerebral vessels independently causing a thalamic stroke and hypoperfusion of the cortex. During the past years a consensus is growing with regard to the explanatory power of the diaschisis hypothesis. Supporting evidence for this hypothesis is provided by several studies describing a depression of regional neuronal metabolism and cerebral blood flow in functionally connected brain regions (Hillis et al., 2002, 2004; De Boissezon et al., 2005). On the basis of these data, diverse theoretical models have been developed in which the thalamus forms part of a cortico-striato-pallido-thalamocortical loop (Mesulam, 2000; Exner et al., 2001; Mitchell and Dalrymple-Alford, 2006).

During the past decades cognitive and behavioural symptoms have been amply documented in patients with vascular thalamic lesions. Since 1980, more than 600 cases with vascular thalamic lesions have been reported but a systematic and critical review of the available data is lacking. Based on a stringent methodology we performed an in-depth analysis of the neurobehavioural and neurocognitive characteristics of the cases with isolated unilateral and bilateral vascular thalamic damage reported in the literature between 1980 and 2008. The primary aim of our study is to critically review the speech and language characteristics and to discuss the issue of 'thalamic aphasia' associated with unilateral or bithalamic lesions. In addition, a descriptive analysis of the neuropsychological (and affective) symptoms following thalamic lesions is aimed at.

2. Methods

Case reports describing adults with uni- and bilateral thalamic lesions were identified via electronic databases (e.g., Pubmed, Web of Science) and bibliography guided retrieval in the English, French and German literature. We used the following key words to perform the search in electronic databases: 'unilateral thalamic infarction', 'unilateral thalamic haemorrhage', 'left thalamic infarction', 'left thalamic haemorrhage', 'right thalamic infarction', 'right thalamic haemorrhage', 'bilateral thalamic infarction', 'bilateral thalamic haemorrhage', 'thalamic aphasia' and 'thalamic amnesia'.

Only adult cases with vascular thalamic lesions published in scientific journals were selected for further analysis when reference was made to cognition. 618 case descriptions were identified that met these criteria (Appendix 1). Abstracts, letters to the editor, comments on articles, congress proceedings, poster presentations, etc. were not taken into consideration.

All cases recruited for our study ($n = 618$) (Appendix 1) were critically evaluated according to four additional selection criteria: 1) lesion strictly confined to the thalamus as confirmed by CT scan or MRI of the brain, 2) standardized assessment of language skills, 3) evaluation of clinical data according to a time frame model for the study of vascular cognitive phenomena (Mazzocchi and Vignolo, 1979) encompassing findings in the lesion phase of the stroke (3 weeks until 4 months post-stroke) and 4) right-handedness (Fig. 1).

2.1. *Rationale for the adopted criteria*

2.1.1. *Vascular thalamic lesions in adults*

Vascular ischaemic and haemorrhagic lesions are often considered the aetiology of preference to establish anatomoclinical correlations in human neurobehavioural research (Mazzocchi and Vignolo, 1979; Alexander, 1989). Indeed, in contrast to head trauma, infections, neurodegenerative diseases, tumours and abcesses which are typically accompanied by diffuse cerebral damage, cerebral infarctions and haemorrhages are associated with focal tissue damage. As such, ischaemic brain lesions and intracerebral haemorrhages are considered to offer a reliable basis to build anatomoclinical correlations when studied after the acute phase of the stroke when most of the mass lesion effects have resolved.

Our review of the literature is confined to adult cases because: 1) prominent dynamic shifts in the cerebral organisation occur in children during language development and 2) uncertainty exists about the activation mechanisms of brain

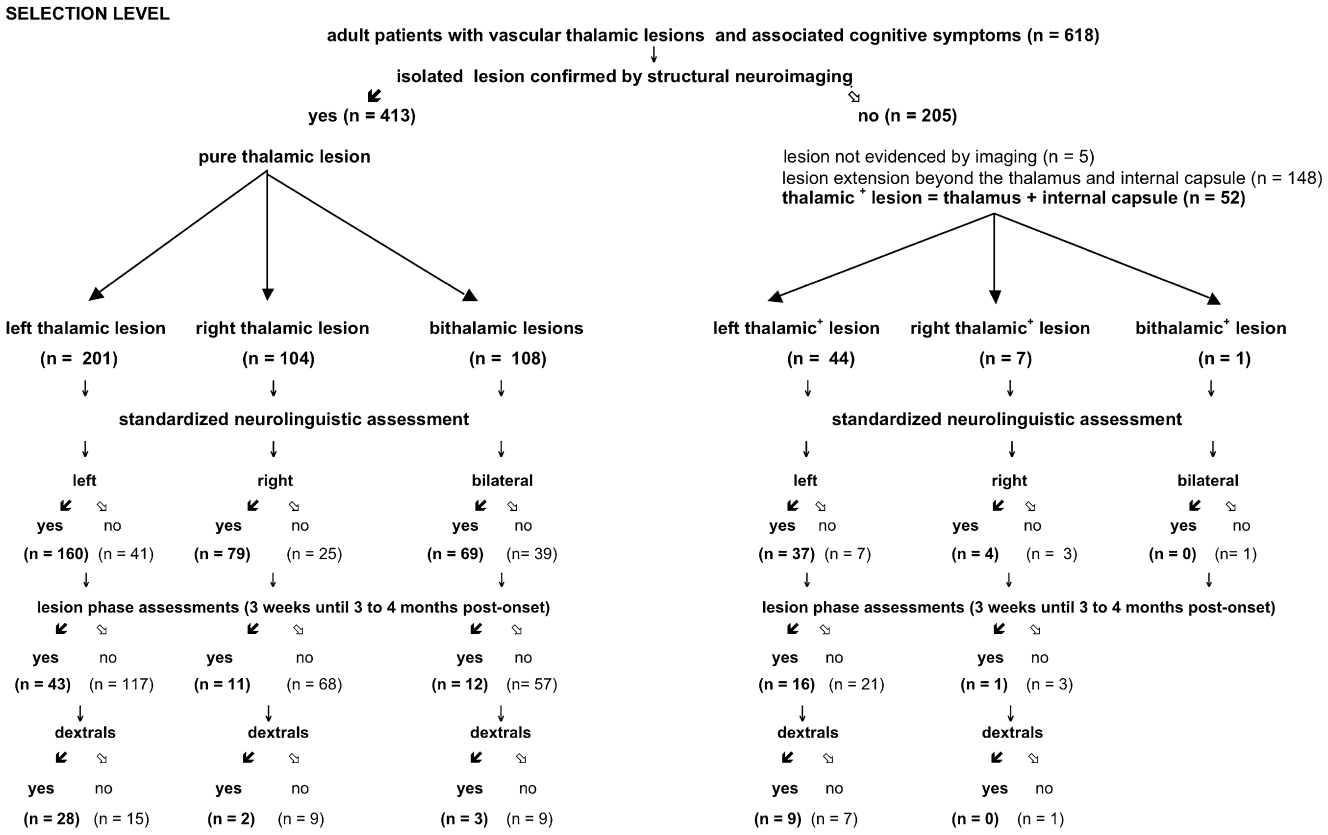

Fig. 1 – Paradigm of diagnostic criteria for vascular thalamic lesions ($n = 618$). ↙ = cases included in the analysis following the criteria of the paradigm; ↘ = cases NOT included in the analysis.

plasticity during childhood (Neville and Bavelier, 1998; Holland et al., 2007).

2.1.2. *Evidence of isolated thalamic damage confirmed by structural neuroimaging*

Because lesion-aphasia studies at the end of the 1970s and the beginning of the 1980s for the first time in vivo demonstrated the neuroanatomical substrate of subcortical speech and language disturbances by means of CT, we decided to take 1980 as a starting-point to review the literature (Cappa and Vignolo, 1979; Damasio et al., 1982; Mohr, 1983; Naeser, 1983; Abutalebi et al., 2008).

For the purpose of our study, confirmation of a thalamic lesion involving one or both thalami as documented by structural neuroimaging (CT or MRI) was required. Involvement of the adjacent internal capsule in the lesion configuration was not considered as an exclusion criterion for the selection of our study population. Patients with thalamic damage extending to the internal capsule were denoted as 'thalamic^{+}'.

Population based studies of healthy persons aged 65 and older have demonstrated that white matter lesions may occur in one third to 80% of the subjects (Breteler et al., 1994; Longstreth et al., 1996 for the Cardiovascular Health Study Collaborative Research Group). In the Rotterdam Scan Study, 1904 MRIs of randomly selected non-demented persons aged 60–90 years were scored for cerebral white matter lesions. This study revealed that: 1) only 8% of all subjects did not have subcortical white matter lesions, 2) 20% had no periventricular white matter lesions and 3) only 5% had no white matter lesions in either of these locations (De Leeuw et al., 2001). The high prevalence of lesions in the subcortical and periventricular white matter urged us to include case reports of patients aged 65 years or older with lesions of the thalamus and of the subcortical white matter and/or the periventricular white matter.

Thalamic cases with mesencephalic involvement were excluded in our study because mesencephalic lesions often induce dysarthria. In a study on the clinical manifestations of pure midbrain infarctions, Kim and Kim (2005) showed that in addition to ataxia, oculomotor and sensory disturbances, dysarthria was present in 55% ($n = 22$) of the 40 cases.

In order to deduce clear-cut anatomoclinical correlations, patients with prominent cortical atrophy, patients who sustained prior (sub)cortical brain damage, patients with recurrent thalamic lesions, patients with additional basal ganglia lesions and patients with additional hypothalamic lesions were excluded because non-thalamic damage would complicate the interpretation of the results.

2.1.3. *Formal assessment of language skills*

Availability of standardized neurolinguistic test data was adopted as a crucial criterion for further analysis. In agreement with this criterion, case descriptions were accepted for further analysis when language data were collected by means of standardized tests such as the Boston Diagnostic Aphasia

Examination (BDAE) (Goodglass and Kaplan, 1972, 1983), the Multilingual Aphasia Examination (MAE) (Benton and Hamsher, 1978), the Western Aphasia Battery (WAB) (Kertesz et al., 1979; Kertesz, 1982), the Standard Language Examination (SLE) (Basso et al., 1979), the Standard Language Test of Aphasia (SLTA) (Takeda, 1977), the Boston Naming Test (BNT) (Kaplan and Goodglass, 1983) and the Graded Naming Test (GNT) (McKenna and Warrington, 1983). In addition, articulatory features, prosodic characteristics and speech dynamics were evaluated as well. Speech was categorized as dysarthric when more than one phono-articulatory feature (respiration, articulation, phonation, resonance) was deficient. Impairment of speech prosody and reduction of spontaneous speech were labeled on the basis of the author's observation.

Analogous to the criterion of formal language assessment, claims relating to neuropsychological disturbances (praxis, gnosis, attention, memory, intelligence and executive functions) had to be substantiated by formal test data. Case reports in which the description of neurocognitive symptoms was not substantiated by formal test data were not included for further analysis. Since emotional-affective symptoms and personality changes are generally only documented at the descriptive level, the criterion of formal test justification was not applied to the description of symptoms at the pure behavioural and affective level (auto-activation deficits, apathy, emotional lability, etc.).

2.1.4. *Assessment of clinical data in the lesion phase*

Case reports evaluating neurocognitive symptoms were selected for further analysis when data were obtained in the "lesion phase" of the stroke. The intermediate phase post-stroke (3 weeks to 4 months) (lesion phase) is considered to be the most reliable for establishing brain–behaviour relationships as diaschisis, which often has major clinical repercussions in the acute phase of the stroke, is less important and functional compensation is still minimal. In order to allow construction of sufficiently reliable anatomoclinical correlations, care has been taken in the present review to select only cases in which neurobahavioural data were formally obtained during the lesion phase.

Absence or presence of linguistic features (fluency, language comprehension, repetition, naming, reading, writing, dysarthria and dysprosodia) and nonverbal cognitive symptoms (visual attention, praxis, gnosis, calculia, orientation, global intellectual functioning, attention, memory, executive functions, behaviour and/or mood alterations) of the 'reliable cases' was listed with a focus of attention to the degree of impairment. A question mark was added in the appendices whenever a case report lacked description of one of these features.

2.1.5. *Manual preference*

Right-handedness was added as an additional criterion because a consensus exists in the literature that the thalamus is functionally lateralised. In dextrals, studies have shown that verbal processes are mediated by the left thalamus (Ojemann and Ward, 1971; Sodeyama et al., 1995; Bhatnagar and Mandybur, 2004), and visuo-spatial abilities and nonverbal information processing by the right thalamus (Van Der Werf et al., 1999; Ortigue et al., 2001; Marey-Lopez et al., 2002; Summers, 2002; De Witte et al., 2008a, 2008b). However, formal assessment of hand preference could not be applied as an inclusion criterion since handedness was only formally investigated in a minority of cases (Rousseaux et al., 1986, 1995; Della Sala et al., 1997).

2.2. *Analysis of the neurobehavioural symptoms*

At the *neurolinguistic* level, the language symptoms described in the lesion phase were analysed according to eight speech/language features: 1) oral verbal fluency, 2) language comprehension, 3) repetition, 4) naming, 5) reading, 6) writing, 7) dysarthric symptoms and 8) prosody. The degree of impairment was evaluated on a four-point scale: 0 = none, 1 = mild, 2 = moderate and 3 = severe impairment (Appendices 2 and 3).

Based on a close analysis of available data in the literature (Cambier et al., 1983; Crosson, 1984; Fasanaro et al., 1987; Bogousslavsky et al., 1986a, 1986b; Démonet et al., 1989; Ackermann et al., 1993; Özeren et al., 1994; Kumar et al., 1996; Ure et al., 2001; Kuljic-Obradovic, 2003; Radanovic and Scaff, 2003; Bruce et al., 2004; Hillis et al., 2004), six cardinal features were selected that characterise thalamic aphasia as a typical aphasic syndrome: 1) fluent oral output (severity score: 0), 2) normal or mildly impaired verbal comprehension (severity score: 0–1), 3) normal or mildly impaired repetition (severity score: 0–1), 4) moderate to severe anomia characterised by semantic paraphasias, neologisms and perseverations (severity score: 2–3), 5) hypophonia and/or mild articulation deficits (dysarthria symptoms, severity score: 1) and 6) reduction of spontaneous speech or verbal aspontaneity (severity score: 2–3). A diagnosis of thalamic aphasia was made in our study when at least four of the six features were met.

To construct anatomoclinical configurations a statistical analysis was performed to measure the strength of association between the presence of thalamic aphasia and the lateralisation of the vascular lesion (χ^2 test and Nagelkerke's R-square).

On the *neuropsychological* level, a variety of deficits such as visual neglect, constructional, ideational, ideomotor and oral apraxia, acalculia as well as impaired attention, disrupted memory, disorientation, impaired intelligence and executive dysfunctions have been reported. Analogous to the speech–language characteristics, the same scale was used to define the degree of impairment. Other neurocognitive impairments such as limb apraxia, digital agnosia, hemisomatognosia, finger agnosia, astereognosia, auditory agnosia, prosopagnosia and deficient left–right discrimination are included in Appendices 2 and 4.

Thalamic lesions have been associated with *behavioural and/or mood alterations* (Bewermeyer et al., 1985; Bogousslavsky et al., 1991; Ackermann et al., 1993; Van Domburg et al., 1996; Engelborghs et al., 2000; Carrera et al., 2004; Habib, 2004; Carrera and Bogousslavsky, 2006; De Witte et al., 2006, 2008a, 2008b). Since these phenomena are generally not investigated by means of formal instruments, case reports containing descriptions of a post-stroke behavioural and/or mood modification in the lesion phase were included.

Symptoms were listed according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV, 2001) classification of the American Psychiatric Association (Appendix 5).

3. Results

618 case reports describing patients with vascular thalamic lesions were selected for this study (Appendix 1). The corpus comprised 135 patients with haemorrhages (=21.8%) and 483 patients with infarctions including ischaemic lesions and deep venous thrombosis (=78.2%). Of the 483 cases with thalamic infarctions, 151 patients were excluded because the lesion extended beyond the boundaries of the thalamus ($n = 148$)[1] or because the lesion was not shown on structural neuroimaging ($n = 5$).[2] As a result, 465 of the 618 adult cases (=75.2%) exhibited a lesion either restricted to the thalamus or a lesion slightly encroaching upon the internal capsule (Fig. 1).

3.1. *Demographic characteristics*

The demographic characteristics of the study corpus of 465 adult cases with isolated vascular thalamic damage are illustrated in Table 1.

The majority of the patients were men (=274/465; 58.9%)[3] and 41.1% of the patients were women (=191/465).[4] Statistical analysis disclosed a significant gender difference ($\chi^2 = 14.82$, $df = 1$, $p = .00$) with a male–female ratio of 1.43. Mean age of the patients was 58.2 years (SD ± 13.7 years; range 18–89 years), with a non-significant trend for men being younger than women ($df = 1$, $p = .22$) (Table 1).

Almost three-quarter of the study population suffered from a thalamic infarction (=348/465; 74.8%)[5] while the remaining 117 patients had a thalamic haemorrhage (25.2%).[6] As such, the study corpus consisted of significant more patients with infarctions than haemorrhages ($\chi^2 = 1.15$, $df = 1$, $p = .00$) (Table 1).

Mean age of the patients with infarctions was 57.3 years (SD ± 14.1 years; range 18–89) and 60.7 years (SD ± 12.1 years; range 24–86) for the patients with haemorrhages. Both groups significantly differed in terms of mean age ($\eta = .11$, $df = 1$, $p = .021$). There was no significant gender difference with regard to vascular aetiology ($\chi^2 = .00$, $df = 1$, $p = .99$) (Table 1).

A left thalamic lesion was found in 52.9% of the study group (=246/465).[7] 111 patients (=23.9%) had a right thalamic lesion[8] and 108 out the 465 patients contracted bilateral thalamic damage (=23.2%)[9] (Table 1).

[1] Case nrs. 17–19, 28, 30, 38, 40–41, 44, 47, 50, 52–53, 55, 84–85, 111, 113, 116–118, 120, 122–123, 126–127, 130, 133–134, 136–140, 143–146, 152, 154, 158–159, 179, 182, 188, 204, 206, 208, 211–212, 219–220, 223–225, 273, 276, 290, 294, 297, 299–301, 311, 316, 320, 326, 342, 353, 356, 362, 364–366, 369, 371, 376, 385, 387, 389–390, 394–395, 399, 416, 418, 436, 439, 441, 443, 453–455, 457, 472–477, 480, 484–485, 489–491, 494–495, 507–508, 510, 514, 523, 526–527, 532–534, 538, 540–541, 543–547, 550, 557, 566, 574, 576, 580–582, 584–586, 589–592, 594, 598–600, 610, 617–618.

[2] Case nrs. 5, 34–37.

[3] Case nrs. 1, 3–4, 6, 8–12, 15, 18, 22, 31–33, 39, 42–43, 46, 48–49, 51, 56, 62, 67–73, 75–78, 80–81, 83, 90–94, 97–98, 100–102, 104–107, 109–110, 114, 124–125, 132, 135, 141, 147–149, 151, 153, 155, 157, 160–161, 164–167, 169, 174, 177–178, 180, 183–185, 187, 189, 192–193, 199–200, 202, 205, 209–210, 214–216, 218, 226–237, 243–247, 250, 252, 254–255, 258, 262–264, 269, 274, 277–280, 282–283, 287, 289, 291, 296, 302–303, 308, 310, 312–315, 319, 322–325, 330, 332–333, 335–340, 342, 345–346, 348–352, 354–355, 358–360, 367, 370, 372–373, 375, 379–382, 384, 386, 388, 392, 396, 401–403, 405–407, 410–415, 417, 420, 424, 427–428, 433, 437–438, 442, 445, 447–450, 452, 456, 459, 461–465, 468–469, 471, 478, 481, 487–488, 493, 496–499, 501–503, 505, 511–513, 516, 517, 519–522, 525, 528–529, 535, 539, 548, 552, 554, 556, 558, 565, 567, 578–579, 583, 595–597, 601–604, 606, 613–615.

[4] Case nrs. 2, 7, 13–14, 16, 21, 23–27, 29, 45, 54, 57–61, 63–66, 74, 79, 82, 86–89, 95–96, 99, 103, 108, 112, 115, 119, 121, 128–129, 131, 142, 150, 156, 162–163, 168, 170–173, 174–175, 181, 186, 190–191, 194–198, 201, 203, 207, 213, 217, 221–222, 238–242, 248–249, 251, 253, 256–257, 259–261, 265–268, 270–272, 275, 281, 284–286, 288, 292–293, 295, 298, 304–307, 309, 317–318, 321, 327–329, 331, 334, 343–344, 347, 357, 361, 363, 368, 374, 377–378, 383, 391, 393, 397–398, 400, 404, 408–409, 419, 421–423, 425–426, 429–432, 434–435, 440, 444, 446, 451, 458, 460, 466–467, 470, 479, 482–483, 486, 492, 500, 504, 506, 509, 515, 518, 524, 530–531, 542, 549, 551, 553, 555, 568–573, 575, 577, 587–588, 593, 605, 607–609, 611–612, 616.

[5] Case nrs. 10–15, 18, 21–22, 29, 31–33, 42–43, 45–46, 48–49, 51, 54, 56–81, 87, 89, 92, 96–99, 106–110, 112, 114–115, 119, 121, 124–125, 128–129, 131–132, 135, 141–142, 147–148, 153, 156–157, 160, 162–163, 165–169, 171–178, 180–181, 184–187, 202–203, 213–218, 221–222, 226, 228, 232–234, 236, 249–269, 271–275, 277, 287–289, 291–293, 295–296, 298, 302–310, 312–314, 317–319, 321–324, 327–339, 342–351, 355, 357, 360, 363, 367, 369–370, 372, 375, 377–384, 386, 388, 391, 393, 396–398, 402–404, 406–413, 415, 417, 419–427, 432–435, 448, 452, 456, 459–468, 470–471, 478–479, 481–482, 486, 488, 493, 496–505, 512, 520–522, 524–525, 528, 531, 535–537, 539, 542, 548–549, 552–556, 558, 560–565, 567–573, 575, 579, 583, 593, 595–597, 602, 604–609, 611–616.

[6] Case nrs. 1–4, 6–9, 16, 23–27, 39, 82–83, 86, 88, 90–91, 93–95, 100–105, 149–151, 155, 161, 164, 170, 183, 189–201, 207, 209–210, 227, 229–231, 235, 237–248, 270, 278–286, 315, 325, 340, 352, 354, 358–359, 361, 373–374, 392, 400–401, 405, 413, 428–431, 458, 469, 483, 487, 492, 506, 511, 513, 515–520, 551, 559, 601, 603.

[7] Case nrs. 1–4, 6–10, 12, 14–16, 22–27, 29, 31–33, 39, 45–46, 48, 59, 61, 70–80, 83, 86–87, 91, 96–97, 99–105, 119, 121, 124–125, 128–129, 132, 149, 155–157, 160–161, 163–164, 168–173, 175, 177–178, 180, 183–184, 189–194, 201–203, 214–215, 221–222, 227–233, 236–242, 249–250, 252, 254, 256, 259, 262–263, 266–268, 271–272, 274, 277–288, 298, 302, 308–309, 315, 318, 321–322, 324–325, 327, 330–340, 345–349, 351–352, 354, 359, 368, 372–374, 377–383, 391–392, 397–398, 400–407, 417, 428–430, 432, 434–435, 458, 463–464, 468–469, 483, 486–488, 492, 496–499, 506, 509, 511, 517–522, 525, 529, 531, 537, 551, 553, 558, 563–564, 568, 571, 573, 578–579, 588, 593, 607–608, 611, 613–616.

[8] Case nrs. 62–69, 81–82, 92–95, 98, 131, 150–151, 195–200, 209–210, 217–218, 226, 234–235, 243–248, 251, 253, 255, 257–258, 260–261, 264–265, 269–270, 303, 305–307, 317, 323, 342, 350, 358, 360, 370, 375, 386, 388, 396, 408–415, 419, 422–423, 425–426, 431, 433, 456, 466–467, 470–471, 493, 500–504, 512–513, 516, 528, 530, 539, 542, 552, 554–555, 559–562, 565, 569–570, 577, 583, 587, 601.

[9] Case nrs. 11, 13, 18, 21, 42–43, 49, 51, 54, 56–58, 60, 106–110, 112, 115, 135, 142, 147–148, 153, 162, 165–167, 174, 176, 181, 185–187, 205, 213, 216, 275, 289, 291–293, 295–296, 304, 310, 312–314, 319, 328–329, 343–344, 355, 357, 361, 363, 367, 384, 393, 420–421, 424, 427, 437–438, 440, 442, 444–4452, 459–462, 465, 478–479, 481–482, 505, 524, 535–536, 548–549, 556, 567, 572, 575, 595–596, 597, 602–606, 609, 612.

Table 1 – Demographic characteristics of 465 patients with a vascular thalamic lesion.

Thalamic lesions ($n = 465$)	Number	Percentage
Gender		
Male	274	58.9
Female	191	41.1
Aetiology		
Infarction	348	74.8
Haemorrhage	117	25.2
Lesion localisation		
Left thalamic/thalamic +	246	52.9
Right thalamic/thalamic +	111	23.9
Bithalamic/bithalamic +	108	23.2
Age		
Mean age ± SD	58.2 ± 13.7	
Age range	18–89	

No significant difference between men and women was found with respect to lesion lateralisation meaning that men and women have the same chance to develop a unilateral (left or right) or bilateral thalamic lesion ($\chi^2 = .15$, $df = 2$, $p = .93$). Yet, a significant correlation was found between age and lesion lateralisation. Patients with a bilateral thalamic lesion (median age = 55.28; SD ± 15.24 years) were younger than patients with a left (mean age = 58.11; SD ± 12.83 years) or right thalamic lesion (mean age = 61.37; SD ± 13.42) (*Eta coefficient in ANOVA design* = .15, $df = 2$). A significant correlation was found between aetiology and lesion lateralisation. Haemorrhages have a relative tendency to preferentially affect the left thalamus (*Eta coefficient* = .19, *Cramer's V* = .29, $df = 2$) (Cohen, 1988).

3.2. *Selection of 'reliable cases'*

116 of the 465 case reports (=24.9%)[10] were excluded from further analysis since neurolinguistic functions were not investigated on the basis of a standardized method for the assessment of language skills (Fig. 1). Standardized neurolinguistic assessments were performed in 349 patients (=75%). However, in only 83 case reports (=23.8%) a description of symptoms was based on a time frame model. 266 case reports (=76.2%)[11] had to be rejected because time postonset was not specified or because lesion phase data were lacking (Fig. 1). Out of the 83 cases, 42 patients were listed as right-handed (=63.5%). One patient was considered a left-hander (case nr. 388) while in the remaining cases manual preference was not mentioned (Fig. 1 and Appendix 1).

Summing-up, 42 out of 465 (=9%)[12] cases of the isolated thalamic and thalamic$^+$ group matched the requirements for a sufficiently reliable analysis in terms of neurocognitive characteristics and lesion-behaviour relationships.

Table 2 – Neurolinguistic characteristics of the 42 reliable cases with vascular thalamic damage.

Neurolinguistic characteristics	Left thalamic lesions ($n = 37$)	Right thalamic lesions ($n = 2$)	Bithalamic lesions ($n = 3$)
Aphasic symptoms			
Fluency problems	2/31 (6.4%)	0/1	0/2
Comprehension problems	14/32 (43.8%)	0/1	1/2
Repetition problems	5/33 (15.1%)	0/1	1/2
Naming problems	26/36 (72.2%)	1/2	2/2
Reading problems	7/28 (25%)	0/1	0/1
Writing problems	13/20 (65%)	No info	0/1
Dysarthric symptoms	12/39 (30.8%)	No info	1/3
Dysprosodia	1/4	No info	1/2
Reduced spontaneous speech	1/1	No info	1/1
Thalamic aphasia	7/11 (63.6%)	No info	1/1

3.3. *Neurolinguistic analysis*

3.3.1. *Description of the neurolinguistic characteristics*

Analysis of speech and language characteristics was performed in 42 cases with isolated vascular thalamic lesions. As mentioned above, speech and language symptoms were analysed in the lesion phase by means of eight linguistic parameters.

Only one patient (case nr. 513) presented aphasic symptoms (naming disturbances) after a right thalamic lesion. Since this patient is a dextral, he might be regarded as an example of crossed aphasia. Information with regard to dysarthria, dysprosodia and verbal aspontaneity was not provided in the group of patients with right thalamic lesions. As a consequence, the analysis of speech and language characteristics is focused on the reliable cases with left ($n = 37$) and bilateral thalamic involvement ($n = 3$). The results of the analysis are presented in Table 2 at the end of this section (see also Appendix 3). When possible, additional statistical analysis was performed to investigate if significant differences exist between the linguistic symptoms and lesion aetiology (haemorrhage, infarction) in the intermediate phase. Due to the small number of patients in the bithalamic group, statistical analysis was only performed in the left thalamic patient group.

[10] Case nrs. 14–15, 18, 22–25, 54, 62, 64, 70, 77, 82, 106–110, 112, 115, 149–151, 153, 155, 160, 163, 169–171, 181, 184, 213, 277–278, 291–293, 295–296, 298, 302–303, 310, 312–313, 315, 317, 321, 325, 329–330, 340–341, 343, 350–351, 358, 360, 363, 370, 373–375, 384, 386, 391, 393, 398, 419–421, 434–435, 458–460, 462, 464–471, 496, 498, 500–501, 505–506, 524, 528, 531, 542, 548–549, 551, 553–555, 559, 575, 577, 579, 593, 595, 601, 609, 612.

[11] Case nrs. 9, 26–27, 29, 31–33, 39, 43, 46, 48–49, 56–61, 63, 65–67, 69, 72, 75, 78–81, 83, 87, 92–93, 96–99, 102, 119, 121, 124–125, 128–129, 131, 135, 141–142, 147–148, 156, 161–162, 166–168, 172–178, 180, 183, 185–187, 189–201, 203, 209–210, 214–218, 226–228, 232–237, 242, 244–245, 247–250, 254–258, 261, 263–266, 269, 271–272, 274–275, 280–281, 283, 304–309, 313, 318–319, 322–324, 328, 331–339, 346–348, 352, 357, 361, 367–368, 372, 378–383, 392, 396, 400–415, 417, 422–433, 437–438, 440, 442, 444–452, 456, 463, 478–479, 481–483, 486–488, 492–493, 497, 499, 502–504, 509, 511–512, 515–520, 525, 529–530, 535–537, 539, 556, 560–565, 567–572 583, 587–588, 596–597, 602, 604–608, 611, 613–616.

[12] Case nrs. 1–4, 6–8, 10, 12, 42, 45, 68, 71, 73–74, 76, 100–101, 103–104, 114, 132, 157, 202, 279, 282, 284–286, 288, 327, 344–345, 349, 354, 359, 397, 513, 521–522, 578, 603.

3.3.1.1. Fluency. In the left thalamic patient group, two out of the 31 cases in which fluency was looked for (=6.4%; case nrs. 354, 522) presented non-fluent speech; no statistical difference was found between patients with haemorrhagic lesions and patients with infarctions ($\chi^2 = .11$, $df = 1$, $p = .73$). In the bithalamic patient group, consisting of three patients, two cases (nrs. 42, 603) were labeled as fluent. No information was provided for the remaining case (nr. 344).

Consequently, 93.6% of the left (=29/31)[13] and 100% of the bilateral thalamic cases (=2/2) in which fluency was looked for, met the first criterion of thalamic aphasia.

3.3.1.2. Language comprehension. In the lesion phase of the stroke, 56.2% of the left thalamic patient group showed normal language comprehension (=18/32)[14] while 43.8% of the left thalamic cases had language comprehension problems (=14/32).[15] In the left thalamic patient group with comprehension problems, half of the patients (=7/14)[16] showed mild comprehension problems. Respectively four (=4/14)[17] and three patients (=3/14)[18] presented moderate and severe comprehension disturbances. Of the bithalamic cases, one patient (=1/2; case nr. 603) had normal comprehension skills while case nr. 42 presented mild comprehension disturbances.

In the patient group with left thalamic lesions, no significant difference was found between comprehension skills and aetiology ($\chi^2 = .42$, $df = 1$, $p = .513$). As a result, 78.1% (=25/32) of the cases of the left thalamic group and 100% (=2/2) of the cases of the bithalamic group had normal or mildly impaired verbal comprehension and therefore match the second criterion that defines thalamic aphasia.

3.3.1.3. Repetition. In the lesion phase, normal repetition was found in 84.8% of the patients with left (=28/33)[19] and in one of the two patients with bilateral thalamic damage (case nr. 603). Repetition deficits were found in 15.1% of the patients with left (=5/33)[20] thalamic damage. One of the two patients with bilateral thalamic lesions presented with repetition deficits (case nr. 42). Additional statistical analysis disclosed no difference between the patients with a left thalamic haemorrhage and the patients with a left thalamic infarction ($\chi^2 = .01$, $df = 1$, $p = .90$). In the left and bithalamic patient group, the degree of severity varied from mild[21] to severe.[22] In the left thalamic patient group with repetition problems, mild impairments were found in three patients (=3/5).[23] One out of two patients of the bithalamic group displayed mildly impaired repetition skills (case nr. 42).

As such, 93.9% (=31/33) of the left and 100% (=2/2) of the bithalamic patient group correspond to the third touchstone of thalamic aphasia.

3.3.1.4. Naming. Naming was evaluated in 36 out of 37 patients (=97.3%) with left thalamic lesions and all patients (=3/3) with bithalamic damage.

72.2% of the left thalamic cases (=26/36)[24] had anomic problems. 30.8% of these patients displayed mild anomia (=8/26)[25] while the remaining cases had moderate to severe anomic problems.[26] Of the bithalamic cases, two patients (=2/3; case nrs. 42, 603) displayed moderate word-finding difficulties. In the left thalamic patient group, no significant impact of the stroke type was found on naming ($\chi^2 = 2.21$, $df = 1$, $p = .14$).

Consequently, 69.2% (=18/26) of the left thalamic group and 66.7% (=2/3) of the bithalamic group agree with the third criterion of thalamic aphasia that posits moderate to severe naming problems.

3.3.1.5. Reading. 25% of the left thalamic patients had reading problems (=7/28).[27] Reading difficulties fluctuated from mild (case nrs. 4, 6–7), to moderate (case nr. 202), to severe (case nrs. 45, 132, 454). In only one patient with bithalamic damage (case nr. 42), reading was investigated and no distortions were found.

In the left thalamic patient group, stroke type had no impact on reading ($\chi^2 = .31$, $df = 1$, $p = .58$).

3.3.1.6. Writing. 65% of the patients with left thalamic damage (=13/20)[28] showed writing difficulties in the lesion phase. The severity of the writing problems varied from mild[29] to moderate[30] to severe.[31] Statistical analysis revealed no significant difference between patients with haemorrhagic lesions and patients with thalamic infarctions ($\chi^2 = 1.31$, $df = 1$, $p = .25$).

In the bithalamic patient group, writing was only evaluated in one patient (case nr. 42) whose writing skills were normal.

3.3.1.7. Dysarthric symptoms. In 30.8% of the left thalamic (=12/39)[32] and one case report of the bilateral thalamic patient group (=1/3) dysarthric symptoms were reported. In most cases dysarthric symptoms consisted of hypophonia[33] and/or articulation deficits.[34] A more detailed description of speech characteristics was not provided for any of these cases.

In the left thalamic patient group, stroke type had no impact on dysarthric symptoms ($\chi^2 = .0$, $df = 1$, $p = 1.0$).

[13] Case nrs. 1–4, 6–8, 10, 12, 45, 100–104, 132, 157, 202, 279, 282, 284 –286, 288, 345, 349, 359, 397, 521, 578.
[14] Case nrs. 1–4, 6, 100–101, 103–104, 114, 157, 285, 349, 359, 397, 521, 578.
[15] Case nrs. 7–8, 10, 12, 45, 132, 202, 279, 282, 284, 286, 288, 354, 522.
[16] Case nrs. 7, 10, 12, 45, 279, 282, 522.
[17] Case nrs. 8, 202, 284, 286.
[18] Case nrs. 132, 288, 354.
[19] Case nrs. 1–4, 6–7, 10, 12, 45, 73–74, 76, 100–101, 104, 114, 132, 157, 279, 282, 284–286, 349, 359 397, 522, 578.
[20] Case nrs. 8, 103, 202, 288, 354.
[21] Case nrs. 8, 42, 103, 288.
[22] Case nrs. 202, 354.
[23] Case nrs. 8, 103, 288.
[24] Case nrs. 1–4, 6–8, 10, 12, 45, 73–74, 104, 132, 202, 279, 282, 284–286, 288, 327, 354, 359, 522, 578.
[25] Case nrs. 1, 3–4, 10, 104, 279, 285, 359.
[26] Case nrs. 2, 6–8, 12, 45, 73–74, 132, 202, 282, 284, 286, 288, 327, 354, 522, 578.
[27] Case nrs. 4, 6–7, 45, 132, 202, 354.
[28] Case nrs. 1, 3–4, 6–8, 10, 45, 101, 114, 132, 288, 354.
[29] Case nrs. 1, 4, 7, 114.
[30] Case nrs. 3, 10, 101.
[31] Case nrs. 6–8, 45, 132, 288, 354.
[32] Case nrs. 1, 3–4, 6–8, 45, 202, 282, 284, 345, 349, 354.
[33] Case nrs. 202, 282, 284, 354.
[34] Case nrs. 1, 6, 8, 345, 354.

Seven of the left thalamic cases had mild dysarthric speech disturbances (=7/8)[35] while the remaining case report displayed severe articulation problems (case nr. 354). Dysarthric symptoms were mild in one patient with a bithalamic lesion (case nr. 42).

Mild dysarthric symptoms are considered to constitute the fifth criterion of thalamic aphasia. 87.5% (=7/8) of the left thalamic patient group and 100% (=1/1) of the bithalamic patient group are consistent with this assumption.

3.3.1.8. Dysprosodia. Prosodic skills were only mentioned in four[36] of the patients with left thalamic lesions and in one patient with bilateral thalamic damage. Prosodic disturbances were broadly described as 'monotonous speech' (case nr. 42) and 'dysprosodic speech' (case nr. 132). No additional information with regard to the suprasegmental characteristics was provided.

In the left thalamic as well as in the bithalamic patient group, only one patient displayed dysprosodia. In the left thalamic group, case nr. 132 showed moderately impaired prosody. Case number 42 with bilateral thalamic damage respectively presented with mild prosodic disturbances.

3.3.1.9. Other speech/language characteristics. In spite of its relevance to the diagnosis of thalamic aphasia, the presence of verbal aspontaneity (=reduced spontaneous speech production) was only documented in one patient with a left thalamic lesion (case nr. 288) and one patient with bilateral thalamic damage (case nr. 42).

Summing-up, patients with left thalamic lesions fulfill four of the cardinal neurolinguistic characteristics that define thalamic aphasia. In order of their importance, the following speech–language features were found: 1) fluent verbal output, 2) normal to mildly impaired repetition, 3) mild dysarthric symptoms and 4) normal to mildly impaired language comprehension. Despite the small number of cases, the neurolinguistic features found in the bithalamic patient group were identical with the features characteristic for the group of patients with left thalamic strokes.

3.3.2. *Prevalence of thalamic aphasia*

In Section 2.2, thalamic aphasia was defined on the basis of six speech and language symptoms. We advanced the view that the taxonomic label of thalamic aphasia may only apply if at least four of the six defining symptoms are met. Since verbal aspontaneity was only reported in one patient, case reports were selected for further analysis when five of the cardinal features of thalamic aphasia were documented. 11 out of 39 reliable cases (=28.2%) with left thalamic lesions allowed further analysis. In the group of patients with bilateral lesions, only one out of three reliable cases (=33.3%) was sufficiently documented to allow further analysis.

63.6% of the patients with left thalamic lesions (=7/11; case nrs. 1, 6, 8, 45, 282, 284, 288) and case nr. 42 of the patients with bilateral thalamic damage (=1/1) (see Table 2) presented at least four of the five features of thalamic aphasia. As a result, thalamic aphasia affected a majority of the patients with left thalamic lesions. Statistical analysis was performed to measure the strength of association between the presence of thalamic aphasia and lesion lateralisation. There was no significant correlation between the presence of thalamic aphasia and a left or bilateral thalamic lesion localisation ($\chi^2 = .54$, $df = 1$, $p = .46$).

Table 3 – Neurocognitive characteristics of 42 reliable case-reports with thalamic damage.

Neurocognitive symptoms	Left thalamic lesions ($n = 37$)	Right thalamic lesions ($n = 2$)	Bithalamic lesions ($n = 3$)
Visual attention deficits	5/13 (38.5%)	No info	1/3
Praxic disturbances			
Oral apraxia	0/13 (0%)	No info	0/1
Constructional apraxia	9/14 (64.3%)	No info	1/2
Ideational apraxia	2/16 (12.5%)	0/2	0/1
Ideomotor apraxia	2/11 (18.2%)	No info	0/1
Gnostic disturbances			
Visual agnosia	0/2	No info	No info
Anosognosia	0/2	No info	2/2
Acalculia	3/12 (25%)	No info	1/1
Desorientation	2/6 (33.3%)	1/1	3/3
Global intellectual dysfunctioning	4/9 (44.4%)	1/1	2/2
Concentration disturbances	2/8 (25%)	1/1	2/3
Mnestic disturbances	21/21 (100%)	1/2	3/3
Dysexecutive problems	4/4 (100%)	1/1	2/3
Behaviour and/or mood alterations	15/17 (88.2%)	1/2	10/10 (100%)

3.4. *Analysis of neuropsychological symptoms*

As shown in Appendix 4, a variety of neurocognitive deficits have been documented in the 42 reliable cases with an isolated thalamic lesion in the lesion phase. The scale to define the degree of impairment is similar to the scale used in the neurolinguistic analyses (Table 3, Appendix 4).

3.4.1. *Neglect*

A specific statement about inattention was made in 33.3% of the cases (14/42).[37] In the left thalamic and bithalamic patient group, visual attention was examined in a minority of the cases, respectively 30% (=13/39) and 33.3% (=1/3) of the patients. None of the patients with a right thalamic lesion were examined with regard to visual attention (0/2). Auditory, tactile and motor neglect were not recorded in any of the case reports.

Different degrees of visual neglect were found: 1) five[38] out of 13 cases with a left thalamic lesion displayed visual attention deficits. One of these patients (1/5; case nr. 6) had severe visual neglect while the remaining 4 patients (4/5) had mild visual attentional problems. One patient out of three cases

[35] Case nrs. 1, 6, 8, 202, 282, 284, 345.
[36] Case nrs. 45, 132, 202, 349.
[37] Case nrs. 1–4, 6–8, 10, 42, 157, 288, 327, 345, 397.
[38] Case nrs. 1, 3, 6, 8, 397.

with a bilateral thalamic lesion had moderate visual neglect (1/3; case nr. 421).

3.4.2. *Apraxia*

3.4.2.1. ORAL APRAXIA. One third of the patients (=13/42; 30.9%)[39] were examined for oral praxis. No patient presented oral apraxia.

3.4.2.2. CONSTRUCTIONAL APRAXIA. Constructional praxis was investigated in 38.1% of the patient group (=16/42).[40] Nine out of 14 patients with left thalamic lesions (=64.3%)[41] exhibited constructional apraxia with a variable degree of impairment. Five cases of the patient group (=5/9)[42] demonstrated mild constructional apraxia. The other patients (=4/9) showed moderate[43] to severe (case nr. 6) constructional impairments. The case with severe constructional apraxia had also severe impairment of visual attention.

No patient with right thalamic damage was assessed for the presence of constructional praxis.

Mild constructional apraxia was found in one out of two patients with bilateral thalamic injury (case nr. 603).

3.4.2.3. IDEATIONAL APRAXIA. Ideational praxis was evaluated in 11 out of 42 cases (=26.2%).[44] Two out of sixteen patients (case nrs. 6, 8) developed a mild impairment of ideational praxis after a left thalamic stroke. None of the patients with a right thalamic (0/2) or bithalamic lesion (0/1) presented ideational apraxia.

3.4.2.4. IDEOMOTOR APRAXIA. Ideomotor praxis was only investigated in 11[45] out of 37 patients with a left thalamic lesion. Ideomotor praxic skills were not examined in the right thalamic patient group. In the bithalamic patient group, ideomotor praxis was examined in one out of three cases (case nr. 42).

Two out of 11 cases with a left thalamic lesion showed mild ideomotor apraxia (case nrs. 6, 8). These two patients also presented ideational apraxia, constructional apraxia and visual neglect. Case number 42 with bithalamic damage displayed normal ideomotor praxic skills.

3.4.3. *Agnosia*

3.4.3.1. VISUAL AGNOSIA. In two out of 42 cases (=4.8%; case nrs. 157, 327), visual gnosis was evaluated. None of the patients had visuo-gnostic disturbances.

3.4.3.2. ANOSOGNOSIA. None of the patients (0/2; case nrs. 157, 327) with left thalamic lesions in whom anosognosia was looked for displayed the disorder. In the right thalamic patient group, anosognosia was not evaluated. Two patients (2/2) with a bilateral thalamic lesion presented moderate (case nr. 344) or severe anosognosia (case nr. 42).

3.4.4. *Acalculia*

Arithmetics were investigated in 13 of the 42 patients (=30.9%).[46] In three out of 12 cases with left thalamic lesions acalculia was found (=25%). The degree of impairment varied from mild (case nr. 157) to severe (case nrs. 6–7). Artihmetics were not evaluated in the two patients with right thalamic damage.

One patient (=1/1; case nr. 42) with bilateral thalamic injury had mildly impaired calculation skills.

3.4.5. *Desorientation*

Orientation was examined in 23.8% of the reliable cases (=10/42).[47] Desorientation was found in 33.3% of the cases with left thalamic damage (=2/6). These two patients (case nrs. 73–74) showed a moderate degree of impairment.

One case with a right thalamic lesion showed normal orientation skills (=1/1; case nr. 68).

All three patients with bilateral thalamic lesions exhibited orientation problems (=3/3). The degree of impairment varied from mild (case nr. 344) to moderate (case nr. 42) to severe (case nr. 603).

3.4.6. *Global intellectual dysfunction*

In 12 out of 42 cases (=28.6%)[48] a specific statement was made about general intelligence. In the patient group with left thalamic lesions, four out of nine cases presented with a mild (case nr. 71, 327), moderate (case nr. 73) or severe (case nr. 578) global cognitive impairment.

In the right thalamic group, a minimally depressed performance IQ level was reported in one case (=1/1; case nr. 68).

A general cognitive decline was found in two patients with bilateral thalamic lesions (=2/2). Case numbers 344 and 42 respectively presented a mild and moderate global cognitive impairment.

3.4.7. *Attentional disturbances*

In one fourth of the cases attention was examined (11/42 = 26.2%). The majority of patients (8/11 = 72.7%) in whom attention was investigated belonged to the left thalamic patient group. In this group, two out of eight cases (=25%) showed a mild (case nrs. 12, 157) attentional disturbance.

One patient with right thalamic involvement displayed moderate attentional deficits (1/1; case nr. 68).

In the bithalamic patient group, attention was only examined in two patients (2/3 = 66.7%). Case number 42 demonstrated a moderate impairment while case number 603 had severe attentional deficits.

[39] Case nrs. 1–4, 6–8, 42, 157, 202, 288, 327, 397.
[40] Case nrs. 1–4, 6–8, 12, 42, 76, 132, 157, 327, 397, 578, 603.
[41] Case nrs. 1, 3–4, 6–8, 76, 132, 578.
[42] Case nrs. 1, 3–4, 7–8.
[43] Case nrs. 76, 132, 578.
[44] Case nrs. 1–4, 6–8, 42, 157, 327, 397.
[45] Case nrs. 1–4, 6–8, 157, 288, 327, 397.
[46] Case nrs. 1–4, 6–7, 10, 42, 76, 114, 157, 349, 521.
[47] Case nrs. 10, 42, 68, 71, 73–74, 288, 327, 344, 603.
[48] Case nrs. 1–4, 6–8, 10, 14–15, 42, 77, 157, 160, 213, 288, 327, 340, 350, 370, 397, 421, 496, 498, 500–501, 528, 542, 579.

3.4.8. Amnesia

Memory was investigated in respectively 56.7%, 100% and 100% of the cases with left (=21/37),[49] right (=2/2) and bilateral thalamic lesions (=3/3). In the patient group with left thalamic lesions, two patients (=2/21; case nrs. 3, 7) had normal verbal and non-verbal memory. 52.4% (=11/21)[50] of the left thalamic cases showed moderate mnestic disturbances while the remaining eight patients (8/21 = 38.1%)[51] exhibited a severe impairment of memory skills. Except for two patients (case nrs. 71 and 74) who presented with isolated visual anterograde amnesia, all patients exhibited anterograde verbal amnesia (17/19 = 89.5%). In almost half of these cases (8/17 = 47%)[52] the mnestic disorder only affected verbal memory functions. In the other cases, a combination of verbal and visual memory disturbances (6/17 = 35.3%)[53] or retrograde amnesia (2/17 = 21.4%; case nrs. 327, 345) was found.

One patient (=1/2; case nr. 513) with right thalamic damage had severe memory impairments.

All patients with bilateral thalamic injury (=3/3)[54] displayed severe memory impairments. All of these patients presented severe verbal and less severe visual memory deficits.

As expected, all patients in the left thalamic ($n = 3$) and bithalamic group ($n = 1$) with thalamic aphasia displayed memory deficits.

3.4.9. Dysexecutive problems

Only in 8 out of 42 patients (=19%),[55] executive functions were investigated. Executive dysfunctions were found in all cases with left thalamic damage (=4/4, 100%).[56] The patient described by Mori et al. (1986) (case nr. 114) only had mild dysexecutive problems. The remaining patients with left thalamic damage (=3/4)[57] showed a moderate impairment.

One of the patients with a right thalamic lesion displayed severely (case nr. 513) impaired executive functions.

In two out of three patients with bilateral thalamic injury (2/3 = 66.7%; case nrs. 42, 603) a severe disruption of executive function was found.

3.4.10. Behaviour and/or mood alterations

A statement about behaviour and/or mood alterations was made for 75 patients with isolated thalamic lesion. Thirty-three of the 75 patients had a left thalamic lesion,[58] 13 a right thalamic lesion[59] and 29 bilateral thalamic damage.[60] The affective and behavioural symptoms are listed in Table 4. In the left thalamic patient group, 66.7% of the patients displayed affective alterations (=22/33);[61] 63.6% showed behavioural alterations (=21/33)[62] and 30.3% exhibited a combination of both affective and behavioural changes (=10/33).[63] Mood disorders and personality disorders were present in more than one third of the cases (8/22 = 36.4%). Apathy was the most prominent feature within the group of behavioural changes: 90.5% of the patients with a left thalamic lesion (=19/21)[64] developed this type of behavioural modification.

In the right thalamic patient group, approximately 70% of the cases displayed affective changes (=9/13).[65] A post-stroke modification of behaviour was recorded in 13 cases. Five out of the 13 patients presented behavioural changes (=38.5%).[66] A combination of both affective and behavioural changes was only recorded in the patient described by Van Der Werf et al. (1999) (case nr. 396). Analogous to the left thalamic group, mood disorders (6/9 = 66.7%) and apathy (3/5 = 60%) represent the most typical feature in the cluster of affective and behavioural alterations.

Twenty-nine patients with bilateral thalamic lesions were evaluated for affective/behavioural changes. Almost 70% of the patients demonstrated affective alterations (=20/29)[67] while nearly 90% of the patients exhibited behavioural modifications (=26/29).[68] A combination of affective and behavioural changes was recorded in 58.6% of the cases with bilateral thalamic damage (=17/29).[69] Within the group of affective disturbances, impulse control disorders (11/20 = 55%) represent the most prevalent feature, followed by mood disorders (=35%; 7/20) and sleep disorders (7/20 = 35%), in particular hypersomnia. Similar to the case reports with left and right thalamic lesions, apathy constitutes the most typical behavioural change in the group of patients with bithalamic lesions (=80.8%).

Summing-up, affective changes occur in more than two thirds of the patients with unilateral or bilateral vascular thalamic lesions. Within the group of affective alterations, mood disorders represent the most typical feature after right thalamic damage. Patients with left thalamic involvement exhibited rather a combination of mood disorders with personality changes while patients with bilateral thalamic lesions display a combination of impulse control disturbances with mood and sleep disorders. On the behavioural level, apathy constitutes the main feature in

[49] Case nrs. 1–4, 6–8, 12, 71, 73–74, 76, 114, 132, 157, 327, 345, 349, 397, 521, 578.
[50] Case nrs. 1–2, 4, 8, 71, 73–74, 132, 157, 349, 397.
[51] Case nrs. 6, 12, 76, 114, 327, 345, 521, 578.
[52] Case nrs. 73, 114, 132, 157, 349, 397, 521, 578.
[53] Case nrs. 1–2, 4, 6, 8, 12.
[54] Case nrs. 42, 344, 603.
[55] Case nrs. 42, 114, 327, 344, 513, 522, 578, 603.
[56] Case nrs. 114, 327, 522, 578.
[57] Case nrs. 327, 522, 578.
[58] Case nrs. 1, 3–4, 6–8, 12, 15, 46, 48, 169–173, 177, 202, 272, 274, 288, 308, 321, 327, 332–337, 345, 464, 498, 529.
[59] Case nrs. 226, 305–307, 317, 323, 386, 396, 412–413, 433, 500, 528.
[60] Case nrs. 42, 49, 106, 115, 135, 153, 166, 176, 181, 185–186, 213, 289, 312–314, 319, 328, 343–344, 355, 357, 363, 393, 421, 461, 465, 597, 603.
[61] Case nrs. 1, 3–4, 6–8, 15, 46, 172–173, 177, 308, 321, 327, 333, 335–337, 345, 464, 498, 531.
[62] Case nrs. 12, 15, 46, 48, 169–172, 202, 272, 274, 288, 327, 332–337, 345, 464.
[63] Case nrs. 15, 46, 172, 327, 333, 335–337, 345, 464.
[64] Case nrs. 12, 15, 46, 48, 169–172, 202, 272, 274, 288, 327, 333–335, 337, 345, 464.
[65] Case nrs. 305–307, 317, 386, 396, 433, 500, 528.
[66] Case nrs. 226, 323, 396, 412–413.
[67] Case nrs. 42, 49, 115, 135, 153, 176, 185–186, 213, 289, 312–313, 319, 344, 355, 363, 393, 461, 465, 597.
[68] Case nrs. 42, 49, 106, 115, 135, 153, 166, 176, 181, 213, 289, 312–314, 319, 328, 343–344, 355, 357, 393, 421, 461, 465, 597, 603.
[69] Case nrs. 42, 49, 115, 135, 153, 176, 213, 289, 312–313, 319, 344, 355, 363, 461, 465, 597.

Table 4 – Affective-behavioural alterations in 75 cases with thalamic involvement.

Affective-behavioural alterations	Left thalamic lesions ($n = 33$)	Right thalamic lesions ($n = 13$)	Bithalamic lesions ($n = 29$)
Affective alterations	22/33 (66.7%)	9/13 (69.2%)	20/29 (68.9%)
Mood disorders (depression, euphory, mania)	8/22 (36.4%)	6/9 (66.7%)	7/20 (35%)
Anxiety disorders	4/22 (18.2%)	1/9	–
Eating disorders (bulemia)	1/22	–	1/20
Sexual disorders (hypersexuality)	–	2/9	3/20
Sleep disorders (hypersomnia)	–	–	7/20 (35%)
Impulse control disorders (disinhibition, etc.)	3/22 (13.6%)	1/9	11/20 (55%)
Psychotic disorders (hallucinations, paranoia)	4/22 (18.2%)	–	–
Personality disorders (emotional lability, etc.)	8/22 (36.4%)	–	5/20 (25%)
Behavioural alterations	21/33 (63.6%)	5/13 (38.5%)	26/29 (89.6%)
Apathy	19/21 (90.5%)	3/5 (60%)	21/26 (80.8%)
Unawareness	6/21 (28.6%)	2/5 (40%)	7/26 (26.9%)
Affective-behavioural alterations	10/33 (30.3%)	1/13 (7.7%)	17/29 (58.6%)

patients with unilateral as well as bilateral thalamic lesions. Since apathy is present in more than 80% of the patients with left thalamic and bilateral thalamic lesions, this symptom represents a typical behavioural feature of thalamic injury. A combination of affective and behavioural alterations is mainly found after bilateral thalamic damage (=58.6%) followed by left (=30.3%) and right thalamic lesions (=7.7%).

In conclusion, the most frequent neuropsychological symptoms of patients with left thalamic lesions are: constructional apraxia, amnestic disturbances, dysexecutive problems and behavioural and/or mood alterations. After bilateral thalamic lesions, patients display a more typical cluster of neurocognitive symptoms characterised by constructional apraxia, anosognosia, desorientation, global intellectual dysfunctioning, attentional problems, amnestic disturbances, dysexecutive problems and behavioural and/or mood alterations. Since neuropsychological symptoms were only partly investigated in two of the patients with right thalamic damage, no conclusions can be made for this group.

4. Discussion

In agreement with Del Mar Saez de Ocariz et al. (1996), who studied patients with MRI-confirmed thalamic strokes, our study reveals a similar distribution of thalamic stroke typology. In both cohorts, approximately 75% of the patients suffered from a thalamic infarction while the remaining 25% had a thalamic haemorrhage. In comparison to epidemiologic stroke data, the incidence of haemorrhages in the thalamus is higher than in other supratentorial brain structures (25% vs 15–17% in common stroke) (the Internet stroke centre for professionals at Washington University, the foundation for Education and Research in Neurological Emergencies).

The demographic data of our study corpus confirm the conclusions of the Mexican study (Del Mar Saez de Ocariz et al., 1996) showing a lower median age of thalamic stroke patients than in non-thalamic stroke patients (59.7 years, range 45–84 years in the Mexican study; 58.2 years, range 18–89 years in the review corpus; Durkin and Briley, 2001, mean age = 76 years in the general stroke population). However, with regard to gender distribution our data do not corroborate the findings of Del Mar Saez de Ocariz et al. (1996) who recorded a higher incidence of men (67% vs 58.9% in our corpus).

In our study corpus, almost 90% of the patients displayed a left thalamic lesion. The remaining group respectively consisted of two patients with right thalamic damage and three patients with bilateral thalamic lesions. Statistical analysis revealed a moderate to strong correlation between aetiology and lesion localisation: thalamic haemorrhages preferentially occur in the left hemisphere.

Analysis of neurocognitive characteristics of our study population was restricted to 42 reliable cases who fulfilled the four inclusion criteria of the cascade paradigm. An important part of this review consisted of an analysis of the neurolinguistic symptoms following vascular thalamic damage. Our analyses confirm the long-standing view that: 1) the thalamus plays a role in language processing and 2) a laterality effect exists with regard to the contribution of the thalamus to high-level linguistic abilities (Penfield and Roberts, 1959; Ojemann, 1975; Maeshima et al., 2001; Whelan and Murdoch, 2005). Only one case report with right thalamic involvement (case nr. 513) – which is probably a case of crossed aphasia – displayed aphasic symptoms. As a consequence, in this review thalamic crossed aphasia in dextrals (CAD) (1/73 = 1.36%) is proportional to the incidence of CAD in the general dextral population following a right hemisphere lesion (=1–4%) (Mariën et al., 2004; De Witte et al., 2008a, 2008b).

Because the semiological characteristics of thalamic aphasia remain under debate (Kuljic-Obradovic, 2003; Radanovic and Scaff, 2003; Kirshner and Jacobs, 2008; Wahl et al., 2008), the key challenge of this review was to investigate whether or not a semiological prototype of thalamic aphasia could be identified on the basis of a stringent analysis of cases described in the literature. Six linguistic parameters were selected to investigate the neurolinguistic characteristics in more detail. On the basis of the findings in the literature (Cambier et al., 1983; Crosson, 1984; Fasanaro et al., 1987; Bogousslavsky et al., 1986a, 1986b; Démonet

et al., 1989; Ackermann et al., 1993; Özeren et al., 1994; Kumar et al., 1996; Ure et al., 2001; Kuljic-Obradovic, 2003; Radanovic and Scaff, 2003; Bruce et al., 2004; Hillis et al., 2004), we adopted the diagnosis of thalamic aphasia as a clinical entity within the group of subcortical aphasias and as semiological distinct complex from the cortical aphasias in case at least four out of the six following operational criteria were met: 1) fluent output, 2) normal or mildly impaired comprehension skills, 3) normal or mildly impaired repetition, 4) moderate to severe anomia characterised by semantic paraphasias, neologisms and perseverations, 5) hypophonia and/or mild articulation deficits and 6) reduction of spontaneous speech or verbal aspontaneity. Almost two thirds of the patients (=7/11; 63.6%) with left thalamic lesions and one patient (=1/1) with bilateral thalamic damage met these requirements. As the majority of the cases presented with the typical cluster of symptoms, our review data indicate that a diagnosis of thalamic aphasia is not only grounded on the neuroanatomic localisation of the aphasiogenic lesion but also results from a typical configuration of aphasic symptoms (Özeren et al., 1994; Kuljic-Obradovic, 2003; Hillis et al., 2004). Whelan et al. (2002) and Whelan and Murdoch (2005) identified high-level language skill impairments such as problems with ambiguous sentences, figurative language, recreating sentences, synonym and antonym generation and semantic absurdities in patients with left thalamic damage. Unfortunately, disruption of these high-level linguistic abilities, as well as reduction of spontaneous speech, remains undetected by most of the traditional aphasia tests. As a consequence, a diagnosis of thalamic aphasia might become more frequent when verbal aspontaneity and high-level language skills are more systematically investigated. With regard to the underlying pathophysiological mechanism, functional neuroimaging studies disclosing significant changes of cortical blood perfusion in patients with neurolinguistic deficits following isolated thalamic strokes confirmed the existence of thalamo-cortical loops (Hillis et al., 2002, 2004; De Boissezon et al., 2005). Recently, additional evidence was found in an experimental study with deep brain stimulation (Wahl et al., 2008). The authors showed that semantic and syntactic language analysis is primarily realised in cortico-thalamic networks.

In-depth analysis of non-verbal neuropsychological deficits accompanying vascular thalamic lesions confirms the general view that the thalamus participates in various neurocognitive processes (Winocur et al., 1984; Bogousslavsky et al., 1986a, 1986b; Malamut et al., 1992; Baumgartner and Regard, 1993; Van Der Werf et al., 1999, 2003; Engelborghs et al., 2000; Benabdeljlil et al., 2001; Exner et al., 2001; Summers, 2002; Radanovic and Scaff, 2003; Carrera and Bogousslavsky, 2006; De Witte et al., 2008a, 2008b). In the left thalamic patient group, amnestic problems, executive dysfunctions and behaviour and/or mood alterations were the most frequently observed symptoms. The same pattern of clinical symptoms – but much more prominent and with additional neuropsychological deficits – was found in patients with bithalamic lesions. Over two thirds of the patients with bilateral thalamic damage presented with a typical cluster of neurocognitive disturbances consisting of constructional apraxia, anosognosia, desorientation, global intellectual dysfunction, amnesia, and executive dysfunctions associated with behaviour and/or mood alterations. Analogous to the neurolinguistic features, current neuroimaging findings suggest that areas of cortical diaschisis after thalamic infarction correspond to areas affected by thalamo-cortical fibre loss (Krolak-Salmon et al., 2000; Radanovic and Scaff, 2003; Stenset et al., 2007).

With regard to the functional specialisation of the thalamus in non-verbal processing, our study data reveal that the hypothesis of a functional lateralisation in non-verbal processing is no longer valid. In our study: 1) more than one third (35.3%) of the patients with left thalamic damage also exhibited visual memory disturbances and 44% of the patients with left thalamic lesions displayed in addition to a neurolinguistic disturbance also a typical non-dominant hemisphere disorder (visual neglect, visual memory disorders) and 2) almost one fourth (38.5%) of the patients with a vascular lesion of the left thalamus presented with visual neglect. As a result, our review data suggest that: 1) a left hemisphere specialisation for language skills holds at the thalamic level for right-handed adults, and 2) typical non-dominant hemisphere functions do not seem lateralised at the thalamic level. Consequently, these findings support the idea of a 'lateralised linguistic thalamus' but restate the issue of 'a lateralised neurocognitive thalamus' as several authors have advocated (Bogousslavsky et al., 1986a, 1986b; Baumgartner and Regard, 1993; Van Der Werf et al., 1999; Exner et al., 2001; Marchetti et al., 2005).

The relation between language and cognition at the thalamic level is a complex but controversial issue that helps to understand how cognitive processes interact with language and vice-versa. Due to the complexity of the cortico-striato-thalamo-cortical loops, changes in lesion site influence the affected connections and consequently have functional repercussions on the cerebral cortex through deafferentiation mechanisms (Mesulam, 2000; Exner et al., 2001; Mitchell and Dalrymple-Alford, 2006). Obviously, more research is needed to unravel the neurobiological substrate of the complex relationship between neurobehavioural phenomena and the thalamus.

5. Conclusion

In this paper, the literature on the neurocognitive and behavioural-affective impact of vascular thalamic lesions in right-handed adults is critically reviewed since 1980. By means of a cascade paradigm consisting of four criteria, 42 patients out of a corpus of 616 cases with isolated thalamic lesions were isolated and considered sufficiently reliable to perform further analysis in terms of neurobehavioural and lesion-behaviour characteristics. Neurolinguistic analysis confirmed the view of a lateralisation of language functions at the thalamic level and the presence of 'thalamic aphasia' as a distinct aphasia syndrome. Contrary to the neurolinguistic findings, the findings of the neurocognitive analyses restated the idea of a functional lateralisation of non-verbal cognitive processes.

Appendix 1.
Inventarisation vascular thalamic case reports 1980–2009 ($n = 618$)

Case	Reference	n	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
1	Alexander and LoVerme, 1980, case 1	15	73	M	H	+	+	L	+	+
2	Alexander and LoVerme, 1980, case 2		62	F	H	+	+	L	+	+
3	Alexander and LoVerme, 1980, case 3		72	M	H	+	+	L	+	+
4	Alexander and LoVerme, 1980, case 4		64	M	H	+	+	L	+	+
5	Alexander and LoVerme, 1980, case 5		63	F	H	–	+	L	+	+
6	Alexander and LoVerme, 1980, case 7		69	M	H	+	+	L	+	+
7	Alexander and LoVerme, 1980, case 8		57	F	H	+	+	L	+	+
8	Alexander and LoVerme, 1980, case 9		41	M	H	+	+	L	+	+
9	Alexander and LoVerme, 1980, case 13		60	M	H	+	+	L	–	+
10	Cohen et al., 1980	1	62	M	I	+	+	L	+	+
11	Schott et al., 1980	1	46	M	I	+	+	Bi	+	?
12	Archer et al., 1981	1	57	M	I	th +	+	L	+	+
13	Barbizet et al., 1981	1	43	F	I	+	+	Bi	+	?
14	Lemaire et al., 1981, case 1	3	74	F	I	+	+	L	+	+
15	Lemaire et al., 1981, case 2		63	M	I	+	+	L	+	+
16	Lemaire et al., 1981, case 3		67	F	H	th +	+	L	+	?
17	Petit et al., 1981	1	33	F	I	–	+	Bi	+	?
18	Dehaene, 1982, case 1	4	50	M	I	+	–	Bi	–	?
19	Dehaene, 1982, case 2		61	F	I	–	–	Bi	–	?
20	Dehaene, 1982, case 3		51	M	I	–	–	L	–	?
21	Dehaene, 1982, case 4		55	F	I	+	+	Bi	+	?
22	Hammond et al., 1982	1	66	M	I	th +	–	L	–	?
23	Kosten and Rapoport, 1982, case 1	3	69	F	H	+	–	L	–	+
24	Kosten and Rapoport, 1982, case 2		69	F	H	+	–	L	–	+
25	Kosten and Rapoport, 1982, case 3		82	F	H	+	–	L	–	+
26	Mazaux and Orgogozo, 1982, case 1	5	56	F	H	th +	+	L	–	+
27	Mazaux and Orgogozo, 1982, case 3		86	F	H	th +	+	L	–	+
28	Mazaux and Orgogozo, 1982, case 4		46	F	H	–	+	L	–	+
29	Mazaux and Orgogozo, 1982, case 5		78	F	I	th +	+	L	–	–
30	McFarling et al., 1982, case 1	2	52	M	I	–	+	L	–	+
31	McFarling et al., 1982, case 2		18	M	I	+	+	L	?	+
32	Michel et al., 1982	1	54	M	I	+	+	L	?	+
33	Speedie and Heilman, 1982	1	33	M	I	+	+	L	?	+
34	Cambier et al., 1983, case 1	4	53	M	I	–	+	R	+	+
35	Cambier et al., 1983, case 2		62	M	I	–	+	R	–	+
36	Cambier et al., 1983, case 3		68	F	I	–	+	R	–	+
37	Cambier et al., 1983, case 4		68	F	I	–	+	L	–	+
38	Choi et al., 1983, case 1	3	74	M	H	–	+	L	–	?
39	Choi et al., 1983, case 2		50	M	H	+	+	L	–	?
40	Choi et al., 1983, case 3		84	M	H	–	–	R	–	?
41	Goldenberg et al., 1983	1	40	M	I	–	+	L	+	?

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Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
42	Guberman and Stuss, 1983, case 1	**2**	**54**	**M**	**I**	**+**	**+**	**Bi**	**+**	**+**
43	Guberman and Stuss, 1983, case 2		51	M	I	+	+	Bi	–	+
44	Feldmeyer et al., 1984, case 2	4	68	M	I	–	–	R	–	?
45	Gorelick et al., 1984	**1**	**70**	**F**	**I**	**th +**	**+**	**L**	**+**	**+**
46	Graff-Radford et al., 1984, case 1	**5**	**67**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
47	Graff-Radford et al., 1984, case 2		66	F	I	–	+	L	+	+
48	Graff-Radford et al., 1984, case 3		**75**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
49	Graff-Radford et al., 1984, case 4		**69**	**M**	**I**	**+**	**+**	**Bi**	**+**	**+**
50	Graff-Radford et al., 1984, case 5		64	M	I	–	+	R	+	+
51	Winocur et al., 1984	1	38	M	I	+	+	Bi	+	?
52	Bewermeyer et al., 1985, case 2	4	50	M	I	–	–	Bi	–	?
53	Bewermeyer et al., 1985, case 4		38	F	I	–	+	Bi	–	?
54	Biller et al., 1985, case 1	2	79	F	I	+	–	Bi	–	?
55	Biller et al., 1985, case 2		61	F	I	–	–	L	–	?
56	von Cramon et al., 1985, case 1	6	67	M	I	+	+	Bi	?	?
57	von Cramon et al., 1985, case 2		42	F	I	+	+	Bi	?	?
58	von Cramon et al., 1985, case 3		44	F	I	+	+	Bi	?	?
59	von Cramon et al., 1985, case 4		58	F	I	+	+	L	?	?
60	von Cramon et al., 1985, case 5		61	F	I	+	+	Bi	?	?
61	von Cramon et al., 1985, case 6		66	F	I	+	+	L	?	?
62	Friedman, 1985	1	68	M	I	+	–	R	–	+
63	Graff-Radford et al., 1985, case 1	25	48	F	I	+	+	R	–	+
64	Graff-Radford et al., 1985, case 2		78	F	I	+	–	R	–	+
65	Graff-Radford et al., 1985, case 3		64	F	I	+	+	R	–	–
66	Graff-Radford et al., 1985, case 4		58	F	I	+	+	R	–	+
67	Graff-Radford et al., 1985, case 5		66	M	I	+	+	R	–	+
68	Graff-Radford et al., 1985, case 6		**19**	**M**	**I**	**+**	**+**	**R**	**+**	**+**
69	Graff-Radford et al., 1985, case 7		69	M	I	+	+	R	–	+
70	Graff-Radford et al., 1985, case 8		65	M	I	+	–	L	–	+
71	Graff-Radford et al., 1985, case 9		**60**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
72	Graff-Radford et al., 1985, case 10		67	M	I	+	+	L	–	+
73	Graff-Radford et al., 1985, case 11		**75**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
74	Graff-Radford et al., 1985, case 12		**66**	**F**	**I**	**+**	**+**	**L**	**+**	**+**
75	Graff-Radford et al., 1985, case 20		72	M	I	th +	+	L	–	+
76	Graff-Radford et al., 1985, case 21		**47**	**M**	**I**	**th +**	**+**	**L**	**+**	**+**
77	Graff-Radford et al., 1985, case 22		**67**	**M**	**I**	**th +**	**+**	**L**	**+**	**+**
78	Graff-Radford et al., 1985, case 23		58	M	I	th +	+	L	–	+
79	Graff-Radford et al., 1985, case 24		62	F	I	th +	+	L	–	+
80	Graff-Radford et al., 1985, case 25		67	M	I	th +	+	L	–	+
81	Hirose et al., 1985, case 1	6	83	M	I	+	+	R	?	+
82	Hirose et al., 1985, case 2		58	F	H	th +	–	R	–	+
83	Hirose et al., 1985, case 3		75	M	H	th +	+	L	?	+
84	Lepore et al., 1985	1	91	M	I	–	–	Bi	–	?
85	Swanson and Schmidley, 1985	1	27	F	I	–	–	Bi	–	?
86	Baron et al., 1986, case 1	10	40	F	H	th +	+	L	+	?
87	Baron et al., 1986, case 2		60	F	I	+	+	L	–	?
88	Baron et al., 1986, case 3		51	F	H	th +	+	L	+	?
89	Baron et al., 1986, case 4		57	F	I	+	+	L	+	?
90	Baron et al., 1986, case 5		57	M	H	+	+	L	+	?
91	Baron et al., 1986, case 6		53	M	H	th +	+	L	+	?
92	Baron et al., 1986, case 7		53	M	I	+	+	R	–	?
93	Baron et al., 1986, case 8		63	M	H	th +	+	R	–	?
94	Baron et al., 1986, case 9		63	M	H	th +	+	R	+	?
95	Baron et al., 1986, case 10		86	F	H	+	+	R	+	?
96	Bogousslavsky et al., 1986a, 1986b, case 1	3	45	F	I	+	+	L	?	+
97	Bogousslavsky et al., 1986a, 1986b, case 2		74	M	I	+	+	L	?	+
98	Bogousslavsky et al., 1986a, 1986b, case 3		68	M	I	+	+	R	?	+

Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
99	Bogousslavsky et al., 1986a, 1986b	1	72	F	I	+	+	L	–	+
100	**Cappa et al., 1986, case 1**	**5**	**53**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
101	**Cappa et al., 1986, case 2**		**49**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
102	Cappa et al., 1986, case 3		66	M	H	th +	+	L	–	+
103	**Cappa et al., 1986, case 4**		**74**	**F**	**H**	**th +**	**+**	**L**	**+**	**+**
104	**Cappa et al., 1986, case 5**		**65**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
105	Crosson et al., 1986	1	82	M	H	+	+	L	+	?
106	Gerber and Gudesblatt, 1986, case 1	8	72	M	I	+	–	Bi	–	?
107	Gerber and Gudesblatt, 1986, case 2		54	M	I	+	–	Bi	–	?
108	Gerber and Gudesblatt, 1986, case 3		67	F	I	+	–	Bi	–	?
109	Gerber and Gudesblatt, 1986, case 4		82	M	I	+	–	Bi	–	?
110	Gerber and Gudesblatt, 1986, case 5		58	M	I	+	–	Bi	–	?
111	Gerber and Gudesblatt, 1986, case 6		72	F	I	–	–	Bi	–	?
112	Gerber and Gudesblatt, 1986, case 7		78	F	I	+	–	Bi	–	?
113	Gerber and Gudesblatt, 1986, case 8		75	F	I	–	–	Bi	–	?
114	**Mori et al., 1986**	**1**	**41**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
115	**Rondot et al., 1986**	**1**	**45**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
116	Rousseaux et al., 1986, case 1	6	33	F	I	–	+	Bi	–	+
117	Rousseaux et al., 1986, case 2		55	M	I	–	+	Bi	+	+
118	Rousseaux et al., 1986, case 3		42	M	I	–	+	Bi	–	+
119	Rousseaux et al., 1986, case 4		47	F	I	+	+	L	–	+
120	Rousseaux et al., 1986, case 5		48	F	I	–	+	R	–	+
121	Rousseaux et al., 1986, case 6		54	F	I	+	+	L	–	+
122	Vighetto et al., 1986	1	47	M	I	–	–	Bi	–	+
123	Wee, 1986	1	47	M	I	–	–	L	–	+
124	Akiguchi et al., 1987, case 1	8	37	M	I	+	+	L	–	+
125	Akiguchi et al., 1987, case 2		47	M	I	+	+	L	–	+
126	Akiguchi et al., 1987, case 3		66	F	I	–	+	L	–	–
127	Akiguchi et al., 1987, case 4		80	F	I	–	+	L	–	+
128	Akiguchi et al., 1987, case 5		82	F	I	+	+	L	–	+
129	Akiguchi et al., 1987, case 6		65	F	I	+	+	L	–	+
130	Akiguchi et al., 1987, case 7		73	M	I	–	+	L	–	+
131	Akiguchi et al., 1987, case 8		78	F	I	+	+	R	–	+
132	**Fasanaro et al., 1987**	**1**	**59**	**M**	**I**	**th +**	**+**	**L**	**+**	**+**
133	Gentilini et al., 1987, case 1	8	66	M	I	–	+	Bi	?	+
134	Gentilini et al., 1987, case 2		47	F	I	–	+	Bi	?	?
135	Gentilini et al., 1987, case 3		35	M	I	+	+	Bi	?	?
136	Gentilini et al., 1987, case 4		53	M	I	–	+	Bi	?	?
137	Gentilini et al., 1987, case 5		70	F	I	–	–	Bi	–	?
138	Gentilini et al., 1987, case 6		58	M	I	–	+	Bi	?	?
139	Katz et al., 1987, case 6	6	62	M	I	–	+	L	+	–
140	Kobari et al., 1987	1	34	M	I	–	–	Bi	–	+
141	Kritchevsky et al., 1987, case 1	2	32	M	I	+	+	R	–	+
142	Kritchevsky et al., 1987, case 2		25	F	I	+	+	Bi	–	+
143	Lefere et al., 1987, case 1	2	60	F	I	–	–	Bi	–	?
144	Lefere et al., 1987, case 2		70	F	I	–	–	Bi	–	?
145	Meissner et al., 1987, case 1	4	52	M	I	–	+	Bi	–	–
146	Meissner et al., 1987, case 2		69	M	I	–	+	Bi	–	+
147	Meissner et al., 1987, case 3		33	M	I	+	+	Bi	–	+
148	Meissner et al., 1987, case 4		57	M	I	+	+	Bi	–	+
149	Rafal and Posner, 1987, case VM	3	65	M	H	+	–	L	–	?
150	Rafal and Posner, 1987, case VL		67	F	H	+	–	R	–	?

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Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
151	Rafal and Posner, 1987, case NA		54	M	H	th +	–	R	–	?
152	Waterston et al., 1987, case 1	3	68	F	I	–	+	Bi	?	?
153	Waterston et al., 1987, case 2		40	M	I	+	–	Bi	–	?
154	Waterston et al., 1987, case 3		57	F	I	–	+	R	?	?
155	Bellard et al., 1988	**1**	**85**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
156	Bogousslavsky and Regli, 1988, case 3	4	61	F	I	+	+	L	?	–
157	Fensore et al., 1988, case 1	**3**	**67**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
158	Fensore et al., 1988, case 2		44	M	I	–	+	L	+	+
159	Fensore et al., 1988, case 3		62	F	I	–	+	L	+	+
160	Gorelick et al., 1988	**1**	**71**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
161	Hankey and Stewart-Wynne, 1988	1	56	M	H	+	+	L	–	?
162	Lazzarino and Nicolai, 1988	1	55	F	I	+	+	Bi	–	+
163	Mizushima et al., 1988	1	65	F	I	+	–	L	–	?
164	Moonis et al., 1988	1	53	M	H	+	?	L	?	+
165	Nichelli et al., 1988	1	35	M	I	+	+	Bi	+	?
166	Stuss et al., 1988, case 1	3	54	M	I	+	+	Bi	–	+
167	Stuss et al., 1988, case 2		51	M	I	+	+	Bi	–	+
168	Stuss et al., 1988, case 3		70	F	I	+	+	L	–	+
169	Bruyn, 1989, case 18	20	65	M	I	+	–	L	–	?
170	Bruyn, 1989, case 19		60	F	H	+	–	L	–	?
171	Bruyn, 1989, case 20		59	F	I	+	–	L	–	?
172	Ghidoni et al., 1989, case 1	6	55	F	I	+	+	L	–	?
173	Ghidoni et al., 1989, case 2		68	F	I	+	+	L	–	?
174	Ghidoni et al., 1989, case 3		57	M	I	+	+	Bi	–	?
175	Ghidoni et al., 1989, case 4		68	F	I	+	+	L	–	?
176	Ghidoni et al., 1989, case 5		41	F	I	+	+	Bi	–	?
177	Ghidoni et al., 1989, case 6		52	M	I	+	+	L	–	?
178	Ghidoni et al., 1989, case 7		51	M	I	+	+	L	–	?
179	Hennerici et al., 1989	1	53	M	I	–	+	L	?	+
180	Lee et al., 1989	1	57	M	I	+	+	L	?	?
181	Müller et al., 1989	**1**	**41**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
182	Nagaratnam et al., 1989	1	60	F	I	–	–	Bi	–	?
183	Yang et al., 1989, case 3	**3**	**56**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
184	Boiten and Lodder, 1990	1	73	M	I	+	–	L	–	?
185	Graff-Radford et al., 1990, case 1	4	68	M	I	+	+	Bi	–	+
186	Graff-Radford et al., 1990, case 2		19	F	I	+	+	Bi	–	–
187	Graff-Radford et al., 1990, case 3		57	M	I	+	+	Bi	–	+
188	Graff-Radford et al., 1990, case 4		56	M	I	–	+	Bi	–	+
189	Nakamura, 1990, case 1	12	63	M	H	+	+	L	?	+
190	Nakamura, 1990, case 2		48	F	H	+	+	L	?	+
191	Nakamura, 1990, case 3		48	F	H	+	+	L	?	+
192	Nakamura, 1990, case 4		57	M	H	+	+	L	?	+
193	Nakamura, 1990, case 5		61	M	H	+	+	L	?	+
194	Nakamura, 1990, case 6		50	F	H	+	+	L	?	+
195	Nakamura, 1990, case 7		55	F	H	+	+	R	?	+
196	Nakamura, 1990, case 8		63	F	H	+	+	R	?	+
197	Nakamura, 1990, case 9		61	F	H	+	+	R	?	+
198	Nakamura, 1990, case 10		68	F	H	+	+	R	?	+
199	Nakamura, 1990, case 11		52	M	H	+	+	R	?	+
200	Nakamura, 1990, case 12		60	M	H	+	+	R	?	+
201	Robin and Schienberg, 1990, Tl	3	66	F	H	th +	+	L	–	+
202	Robin and Schienberg, 1990, T2		**58**	**M**	**I**	**th +**	**+**	**L**	**+**	**+**
203	Robin and Schienberg, 1990, T3		71	F	I	+	+	L	–	+
204	Sabharwal et al., 1990, case 1	3	55	M	I	–	–	Bi	–	?
205	Sabharwal et al., 1990, case 2		69	M	I	+	–	Bi	–	?
206	Sabharwal et al., 1990, case 3		60	F	I	–	–	Bi	–	?
207	Scialdone, 1990	1	52	F	H	+	–	L	–	?
208	Yasuda et al., 1990	1	62	M	I	–	–	Bi	–	?
209	Au et al., 1991, case 1	12	65	M	H	+	+	R	–	?

Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
210	Au et al., 1991, case 2		61	M	H	+	+	R	–	+
211	Bogousslavsky et al., 1991, case 1	2	61	M	I	–	+	Bi	+	?
212	Bogousslavsky et al., 1991, case 2		64	F	I	–	+	Bi	–	?
213	**Eslinger et al., 1991**	**1**	**58**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
214	Herregodts et al., 1991, case 1	5	54	M	I	+	+	L	?	+
215	Herregodts et al., 1991, case 2		59	M	I	+	+	L	?	+
216	Herregodts et al., 1991, case 3		75	M	I	+	+	Bi	?	+
217	Herregodts et al., 1991, case 4		54	F	I	+	+	R	?	+
218	Herregodts et al., 1991, case 5		53	M	I	+	+	R	?	+
219	Kölmel, 1991	1	56	M	I	–	–	Bi	–	?
220	Lazzarino et al., 1991, case 2	2	74	M	I	–	+	L	?	+
221	Ngai et al., 1991, case 1	5	45	F	I	+	–	L	–	?
222	Ngai et al., 1991, case 4		48	F	I	+	–	L	–	?
223	Nicolai and Lazzarino, 1991, case 1	3	72	F	I	–	+	Bi	–	+
224	Nicolai and Lazzarino, 1991, case 2		55	M	I	–	+	Bi	–	+
225	Nicolai and Lazzarino, 1991, case 3		67	F	I	–	+	Bi	–	+
226	Rousseaux et al., 1991	1	41	M	I	+	+	R	–	+
227	Abe et al., 1992	1	38	M	H	th +	+	L	?	?
228	Baron et al., 1992, case 1	44	52	M	I	+	+	L	–	?
229	Baron et al., 1992, case 2		54	M	H	+	+	L	+	?
230	Baron et al., 1992, case 3		50	M	H	+	+	L	+	?
231	Baron et al., 1992, case 4		58	M	H	+	+	L	+	?
232	Baron et al., 1992, case 6		48	M	I	+	+	L	–	?
233	Baron et al., 1992, case 7		59	M	I	+	+	L	–	?
234	Baron et al., 1992, case 8		59	M	I	+	+	R	–	?
235	Baron et al., 1992, case 9		59	M	H	+	+	R	–	?
236	Baron et al., 1992, case 10		38	M	I	+	+	L	–	?
237	Baron et al., 1992, case 11		47	M	H	+	+	L	–	?
238	Baron et al., 1992, case 12		64	F	H	+	+	L	+	?
239	Baron et al., 1992, case 13		40	F	H	+	+	L	+	?
240	Baron et al., 1992, case 14		51	F	H	+	+	L	+	?
241	Baron et al., 1992, case 15		53	F	H	+	+	L	+	?
242	Baron et al., 1992, case 16		53	F	H	+	+	L	–	?
243	Baron et al., 1992, case 17		76	M	H	+	+	R	+	?
244	Baron et al., 1992, case 18		64	M	H	+	+	R	–	?
245	Baron et al., 1992, case 19		70	M	H	+	+	R	–	?
246	Baron et al., 1992, case 20		61	M	H	+	+	R	+	?
247	Baron et al., 1992, case 21		63	M	H	+	+	R	–	?
248	Baron et al., 1992, case 22		78	F	H	+	+	R	–	?
249	Baron et al., 1992, case 23		58	F	I	+	+	L	–	?
250	Baron et al., 1992, case 24		45	M	I	+	+	L	–	?
251	Baron et al., 1992, case 25		40	F	I	+	+	R	+	?
252	Baron et al., 1992, case 26		74	M	I	+	+	L	+	?
253	Baron et al., 1992, case 27		76	F	I	+	+	R	+	?
254	Baron et al., 1992, case 28		41	M	I	+	+	L	–	?
255	Baron et al., 1992, case 29		63	M	I	+	+	R	–	?
256	Baron et al., 1992, case 30		72	F	I	+	+	L	–	?
257	Baron et al., 1992, case 31		57	F	I	+	+	R	–	?
258	Baron et al., 1992, case 32		53	M	I	+	+	R	–	?
259	Baron et al., 1992, case 33		76	F	I	+	+	L	+	?
260	Baron et al., 1992, case 34		51	F	I	+	+	R	+	?
261	Baron et al., 1992, case 35		72	F	I	+	+	R	–	?
262	Baron et al., 1992, case 36		62	M	I	+	+	L	+	?
263	Baron et al., 1992, case 37		55	M	I	+	+	L	–	?
264	Baron et al., 1992, case 38		64	M	I	+	+	R	–	?
265	Baron et al., 1992, case 39		54	F	I	+	+	R	–	?
266	Baron et al., 1992, case 40		60	F	I	+	+	L	–	?
267	Baron et al., 1992, case 41		57	F	I	+	+	L	+	?

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Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
268	Baron et al., 1992, case 42		59	F	I	+	+	L	+	?
269	Baron et al., 1992, case 43		70	M	I	+	+	R	–	?
270	Baron et al., 1992, case 44		86	F	H	+	+	R	+	?
271	Cole et al., 1992, case 1	5	51	F	I	+	+	L	?	+
272	Cole et al., 1992, case 2		73	F	I	+	+	L	–	+
273	Cole et al., 1992, case 3		67	F	I	–	+	L	–	?
274	Cole et al., 1992, case 4		72	M	I	+	+	L	–	?
275	Cole et al., 1992, case 5		80	F	I	+	+	Bi	?	?
276	De La Sayette et al., 1992	1	30	M	I	–	+	Bi	?	+
277	Gutrecht et al., 1992, case 1	2	63	M	I	+	–	L	–	+
278	Gutrecht et al., 1992, case 2		74	M	H	+	–	L	–	+
279	Ibayashi et al., 1992, case 1	**42**	**44**	**M**	**H**	**+**	**+**	**L**	**+**	**+**
280	Ibayashi et al., 1992, case 2		50	M	H	+	+	L	–	+
281	Ibayashi et al., 1992, case 4		69	F	H	+	+	L	–	+
282	Ibayashi et al., 1992, case 13		**66**	**M**	**H**	**+**	**+**	**L**	**+**	**+**
283	Ibayashi et al., 1992, case 17		57	M	H	+	+	L	–	+
284	Ibayashi et al., 1992, case 19		**72**	**F**	**H**	**+**	**+**	**L**	**+**	**+**
285	Ibayashi et al., 1992, case 21		**65**	**F**	**H**	**+**	**+**	**L**	**+**	**+**
286	Ibayashi et al., 1992, case 22		**65**	**F**	**H**	**+**	**+**	**L**	**+**	**+**
287	Lucchelli and De Renzi, 1992	1	67	M	I	th +	+	L	+	?
288	Maeshima et al., 1992	**1**	**60**	**F**	**I**	**+**	**+**	**L**	**+**	**+**
289	Malamut et al., 1992	1	28	M	I	+	+	Bi	+	?
290	Mennemeier et al., 1992	1	44	F	I	–	+	L	+	–
291	Reilly et al., 1992, case 1	6	67	M	I	+	–	Bi	–	?
292	Reilly et al., 1992, case 2		67	F	I	+	–	Bi	–	?
293	Reilly et al., 1992, case 3		87	F	I	+	–	Bi	–	?
294	Reilly et al., 1992, case 4		40	M	I	–	–	Bi	–	?
295	Reilly et al., 1992, case 5		50	F	I	+	–	Bi	–	?
296	Reilly et al., 1992, case 6		19	M	I	+	–	Bi	–	?
297	Shuaib and Farah, 1992, case 1	2	62	F	I	–	–	Bi	–	?
298	Shuaib and Farah, 1992, case 2		52	F	I	+	–	L	–	?
299	Takahashi et al., 1992	1	55	M	H	–	+	L	–	+
300	Tatemichi et al., 1992, case 2	11	68	M	I	–	–	R	–	?
301	Tatemichi et al., 1992, case 4		74	F	I	–	–	L	–	?
302	Tatemichi et al., 1992, case 6		55	M	I	+	–	L	–	?
303	Tatemichi et al., 1992, case 7		62	M	I	+	–	R	–	?
304	Ackermann et al., 1993	1	64	F	I	+	+	Bi	–	?
305	Baumgartner and Regard 1993, case 1	5	47	F	I	+	+	R	?	+
306	Baumgartner and Regard 1993, case 2		46	F	I	+	+	R	?	+
307	Baumgartner and Regard 1993, case 3		34	F	I	+	+	R	?	+
308	Baumgartner and Regard 1993, case 4		36	M	I	+	+	L	?	+
309	Baumgartner and Regard 1993, case 5		49	F	I	+	+	L	?	+
310	Calabrese et al., 1993	**1**	**46**	**M**	**I**	**+**	**+**	**Bi**	**+**	**+**
311	Guilleminault et al., 1993, case 1	3	43	M	I	–	–	L	–	?
312	Guilleminault et al., 1993, case 2		23	M	I	+	–	Bi	–	?
313	Guilleminault et al., 1993, case 3		28	M	I	+	–	Bi	–	?
314	Hodges and McCarthy, 1993	1	67	M	I	+	+	Bi	–	+
315	Huang and Wang, 1993	1	66	M	H	+	–	L	–	+
316	Kennedy and Murdoch, 1993, case 5	7	56	F	I	–	+	L	?	?
317	Kulisevsky et al., 1993	1	81	F	I	+	–	R	–	+
318	Lisovoski et al., 1993	1	29	F	I	+	+	L	?	+
319	McGilchrist et al., 1993	1	43	M	I	+	+	Bi	?	+
320	Mossuto-Agatiello et al., 1993	1	53	F	H	–	–	L	–	+
321	Noda et al., 1993, case 2	2	46	F	I	+	–	L	–	+
322	Pepin and Auray-Pepin, 1993, case 1	3	51	M	I	+	+	L	–	+

Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
323	Pepin and Auray-Pepin, 1993, case 2		57	M	I	+	+	R	–	+
324	Pepin and Auray-Pepin, 1993, case 3		68	M	I	+	+	L	–	+
325	Rao and Murthy, 1993	1	68	M	H	+	–	L	–	?
326	Scoditti et al., 1993	1	74	M	H	–	–	L	–	?
327	**Clarke et al., 1994**	**1**	**54**	**F**	**I**	**+**	**+**	**L**	**+**	**+**
328	Daum and Ackermann, 1994	1	63	F	I	+	+	Bi	–	?
329	Karacostas et al., 1994	1	28	F	I	+	–	Bi	–	?
330	**Kim et al., 1994**	**1**	**61**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
331	Kotila et al., 1994, case 1	7	48	F	I	+	+	L	–	?
332	Kotila et al., 1994, case 2		57	M	I	+	+	L	–	?
333	Kotila et al., 1994, case 3		39	M	I	+	+	L	–	?
334	Kotila et al., 1994, case 4		41	F	I	+	+	L	–	?
335	Kotila et al., 1994, case 5		44	M	I	+	+	L	–	?
336	Kotila et al., 1994, case 6		48	M	I	+	+	L	–	?
337	Kotila et al., 1994, case 7		50	M	I	+	+	L	–	?
338	Nadeau et al., 1994	1	66	M	I	+	+	L	–	+
339	Parkin et al., 1994	1	48	M	I	+	+	L	?	+
340	**Takayama et al., 1994**	**1**	**52**	**M**	**H**	**+**	**+**	**L**	**+**	**+**
341	Clark and Albers, 1995, case 2	3	47	M	I	+	–	R	–	?
342	Clark and Albers, 1995, case 3		72	M	I	–	–	R	–	–
343	Frey, 1995	1	63	F	I	+	–	Bi	–	+
344	**Haut et al., 1995**	**1**	**40**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
345	**Luchelli et al., 1995; Luchelli and De Renzi, 1992, case GR**	**2**	**67**	**M**	**I**	**th +**	**+**	**L**	**+**	**+**
346	Moreaud et al., 1995	1	65	M	I	+	+	L	?	+
347	Raffaele et al., 1995	1	58	F	I	+	+	L	–	+
348	Rousseaux et al., 1995	1	57	M	I	+	+	L	–	+
349	**Sodeyama et al., 1995**	**1**	**57**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
350	**Weisz et al., 1995, case 1**	**2**	**54**	**M**	**I**	**+**	**+**	**R**	**+**	**+**
351	Weisz et al., 1995, case 2		57	M	I	+	–	L	–	+
352	Chen et al., 1996	1	52	M	H	+	+	L	–	?
353	Gille et al., 1996	1	68	M	I	–	–	L	–	?
354	**Kumar et al., 1996**	**1**	**55**	**M**	**H**	**+**	**+**	**L**	**+**	**+**
355	Van Domburg et al., 1996	1	42	M	I	+	+	Bi	+	?
356	Awada, 1997	1	67	F	I	–	–	Bi	–	+
357	Chatterjee et al., 1997	1	70	F	I	+	+	Bi	?	+
358	Chia, 1997	1	60	M	H	th +	–	R	–	?
359	**Crosson et al., 1997**	**1**	**46**	**M**	**H**	**th +**	**+**	**L**	**+**	**+**
360	**Della Sala et al., 1997**	**1**	**72**	**M**	**I**	**+**	**+**	**R**	**+**	**+**
361	Dromerick et al., 1997	1	73	F	H	+	+	Bi	–	?
362	Fung et al., 1997, case 1	4	62	M	I	–	–	R	–	?
363	Fung et al., 1997, case 2		48	F	I	+	–	Bi	–	?
364	Fung et al., 1997, case 4		65	F	I	–	–	Bi	–	?
365	Fukatsu et al., 1996	1	27	F	I	–	+	Bi	–	+
366	Madan et al., 1997	1	20	F	I	–	–	Bi	–	?
367	Peru and Fabbro, 1997	1	41	M	I	+	+	Bi	–	+
368	Raymer et al., 1997, case 1	2	45	F	I	+	+	L	–	+
369	Raymer et al., 1997, case 2		59	M	I	–	+	L	+	+
370	**Shuren et al., 1997**	**1**	**25**	**M**	**I**	**+**	**+**	**R**	**+**	**+**
371	Tseng and Ryu, 1997, case 1	4	67	F	I	–	+	L	–	?
372	Tseng and Ryu, 1997, case 2		51	M	I	th +	+	L	–	?
373	Berthezène et al., 1998, case 1	2	58	M	H	th +	–	L	–	+
374	Berthezène et al., 1998, case 2		56	F	H	+	–	L	–	+
375	Fukutake and Hattori, 1998	1	49	M	I	+	–	R	–	+
376	Kim et al., 1998	1	55	M	I	–	–	L	–	+
377	Mäkelä et al., 1998, case 1	7	24	F	I	+	+	L	+	?
378	Mäkelä et al., 1998, case 2		43	F	I	+	+	L	–	?
379	Mäkelä et al., 1998, case 3		44	M	I	+	+	L	–	?

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Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
380	Mäkelä et al., 1998, case 4		63	M	I	+	+	L	–	?
381	Mäkelä et al., 1998, case 5		59	M	I	+	+	L	–	?
382	Mäkelä et al., 1998, case 6		54	M	I	+	+	L	–	?
383	Mäkelä et al., 1998, case 7		51	F	I	+	+	L	–	?
384	Miranda and Millar, 1998	1	52	M	I	+	–	Bi	–	?
385	Rousseaux et al., 1998	1	22	F	I	–	+	L	+	–
386	Woodman and Tabatabai, 1998	1	69	M	I	+	–	R	–	+
387	Cordery and Rossor, 1999	1	44	M	I	–	+	R	–	+
388	Ebert et al., 1999	1	65	M	I	+	+	R	+	–
389	Greenenough et al., 1999	1	62	M	I	–	+	Bi	?	?
390	Kao et al., 1999	1	72	F	I	–	–	L	–	–
391	Lampl and Gilad, 1999	1	52	F	I	+	–	L	–	+
392	Manabe et al., 1999	1	43	M	H	+	+	L	–	+
393	Müller et al., 1999	**1**	**69**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
394	Muroi et al., 1999	1	66	M	I	–	–	Bi	–	+
395	Sprengelmeyer et al., 1999	1	50	M	I	–	+	L	?	+
396	Van der Werf et al., 1999	1	44	M	I	+	+	R	–	?
397	Barrett et al., 2000	**1**	**52**	**F**	**I**	**+**	**+**	**L**	**+**	**+**
398	Deleu et al., 2000	1	18	F	I	+	–	L	–	?
399	Engelborghs et al., 2000	1	58	M	I	–	+	Bi	+	+
400	Karussis et al., 2000, case 1	16	79	F	H	+	+	L		?
401	Karussis et al., 2000, case 2		74	M	H	+	+	L	?	?
402	Karussis et al., 2000, case 3		59	M	I	+	+	L	?	?
403	Karussis et al., 2000, case 4		65	M	I	+	+	L	?	?
404	Karussis et al., 2000, case 5		89	F	I	+	+	L	?	?
405	Karussis et al., 2000, case 6		68	M	H	+	+	L	?	?
406	Karussis et al., 2000, case 7		70	M	I	+	+	L	?	?
407	Karussis et al., 2000, case 8		58	M	I	+	+	L	?	?
408	Karussis et al., 2000, case 9		85	F	I	+	+	R	?	?
409	Karussis et al., 2000, case 10		74	F	I	+	+	R	?	?
410	Karussis et al., 2000, case 11		63	M	I	+	+	R	?	?
411	Karussis et al., 2000, case 12		78	M	I	+	+	R	?	?
412	Karussis et al., 2000, case 13		77	M	I	+	+	R	?	?
413	Karussis et al., 2000, case 14		38	M	I	+	+	R	?	?
414	Karussis et al., 2000, case 15		55	M	H	+	+	R	?	?
415	Karussis et al., 2000, case 16		80	M	I	+	+	R	?	?
416	Krolak-Salmon et al., 2000	1	53	M	I	–	+	Bi	+	+
417	Ohno et al., 2000	1	78	M	I	+	+	L	–	+
418	Peru et al., 2000	1	57	M	H	–	+	R	+	+
419	Pradalier et al., 2000	1	54	F	I	+	–	R	–	?
420	Wiest et al., 2000	1	57	M	I	+	–	Bi	–	?
421	Benabdeljlil et al., 2001	**1**	**35**	**F**	**I**	**+**	**+**	**Bi**	**+**	**+**
422	Dagenbach et al., 2001, case LB	6	49	F	I	+	+	R	–	+
423	Dagenbach et al., 2001, case JJ		54	F	I	+	+	R	–	+
424	Dagenbach et al., 2001, case BS		61	M	I	+	+	Bi	–	+
425	Dagenbach et al., 2001, case GR		76	F	I	+	+	R	–	+
426	Dagenbach et al., 2001, case KF		75	F	I	+	+	R	–	+
427	Dagenbach et al., 2001, case JP		83	M	I	+	+	Bi	–	–
428	Fimm et al., 2001, case 1	15	73	M	H	th +	+	L	–	?
429	Fimm et al., 2001, case 2		58	F	H	th +	+	L	–	?
430	Fimm et al., 2001, case 3		79	F	H	+	+	L	–	?
431	Fimm et al., 2001, case 9		46	F	H	th +	+	R	–	?
432	Fimm et al., 2001, case 12		36	F	I	th +	+	L	–	?
433	Inzelberg et al., 2001	1	61	M	I	+	+	R	–	+
434	Küker et al., 2001, case 1	3	49	F	I	th +	–	L	–	?
435	Küker et al., 2001, case 2		58	F	I	+	–	L	–	?
436	Küker et al., 2001, case 3		31	F	I	–	–	L	–	?
437	Kumral et al., 2001, case 1	16	54	M	I	+	+	Bi	–	?
438	Kumral et al., 2001, case 2		73	M	I	+	+	Bi	–	?
439	Kumral et al., 2001, case 3		69	F	I	–	+	Bi	–	?
440	Kumral et al., 2001, case 4		58	F	I	+	+	Bi	–	?

Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
441	Kumral et al., 2001, case 5		74	F	I	–	+	Bi	–	?
442	Kumral et al., 2001, case 6		68	M	I	+	+	Bi	–	?
443	Kumral et al., 2001, case 7		42	M	I	–	+	Bi	–	?
444	Kumral et al., 2001, case 8		60	F	I	+	+	Bi	–	?
445	Kumral et al., 2001, case 9		58	M	I	+	+	Bi	–	?
446	Kumral et al., 2001, case 10		45	F	I	+	+	Bi	–	?
447	Kumral et al., 2001, case 11		70	M	I	+	+	Bi	–	?
448	Kumral et al., 2001, case 12		85	M	I	+	+	Bi	–	?
449	Kumral et al., 2001, case 13		54	M	I	+	+	Bi	–	?
450	Kumral et al., 2001, case 14		35	M	I	+	+	Bi	–	?
451	Kumral et al., 2001, case 15		51	F	I	+	+	Bi	–	?
452	Kumral et al., 2001, case 16		50	M	I	+	+	Bi	–	?
453	Leathem and Martin, 2001	1	20	M	I	–	+	Bi	–	+
454	Miller et al., 2001	1	33	M	I	–	+	R	+	+
455	Nakamura et al., 2001	1	70	F	H	–	–	L	–	+
456	Ortigue et al., 2001	1	86	M	I	+	+	R	–	+
457	Saposnik et al., 2001	1	72	F	H	–	–	L	–	+
458	Takasawa et al., 2001	1	65	F	H	th +	–	L	–	+
459	Weise et al., 2001, case 1	2	61	M	I	+	–	Bi	–	?
460	Weise et al., 2001, case 2		72	F	I	+	–	Bi	–	?
461	Benke et al., 2002	1	38	M	I	+	+	Bi	+	?
462	Comoglu et al., 2002	1	60	M	I	+	–	Bi	–	+
463	Edelstyn et al., 2002, 2006	1	55	M	I	+	+	L	?	+
464	Fukutake et al., 2002	**1**	**48**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
465	Krolak-Salmon et al., 2002	**1**	**57**	**M**	**I**	**+**	**+**	**Bi**	**+**	**+**
466	Kubat-Silman et al., 2002, case MP	6	78	F	I	+	–	R	–	+
467	Kubat-Silman et al., 2002, case BJ		80	F	I	+	–	R	–	?
468	Kubat-Silman et al., 2002, case BV		75	M	I	+	–	L	–	+
469	Kurt et al., 2002, case 2	3	65	M	H	th +	–	L	–	+
470	Marey-Lopez et al., 2002	1	64	F	I	+	–	R	–	+
471	Pack et al., 2002	1	73	M	I	+	–	R	–	+
472	Roitberg et al., 2002	1	48	M	I	–	–	Bi	–	+
473	Summers, 2002	1	59	M	H	–	+	R	–	+
474	Szirmai et al., 2002, case MZ	21	47	M	I	–	+	Bi	+	?
475	Szirmai et al., 2002, case PP		72	F	I	–	+	Bi		?
476	Szirmai et al., 2002, case TF		72	M	I	–	+	Bi	?	?
477	Szirmai et al., 2002, case TA		64	M	I	–	–	L	–	?
478	Szirmai et al., 2002, case EG		76	M	I	+	+	Bi	?	?
479	Szirmai et al., 2002, case GHA		38	F	I	+	+	Bi	?	?
480	Szirmai et al., 2002, case SZJ		73	M	I	–	+	?	?	?
481	Szirmai et al., 2002, case KP		77	M	I	+	+	Bi	?	?
482	Szirmai et al., 2002, case JB		70	F	I	+	+	Bi	?	?
483	Szirmai et al., 2002, case JJ		54	F	H	+	+	L	?	?
484	Szirmai et al., 2002, case KJ		59	M	H	–	+	L	?	?
485	Szirmai et al., 2002, case RL		65	F	I	–	+	L	?	?
486	Szirmai et al., 2002, case KJ		46	F	I	+	+	L	?	?
487	Szirmai et al., 2002, case SzL		75	M	H	th +	+	L	?	?
488	Szirmai et al., 2002, case Ogy		52	M	I	+	+	L	?	?
489	Szirmai et al., 2002, case KA		63	F	I	–	+	L	?	?
490	Szirmai et al., 2002, case CsB		68	F	I	–	+	L	?	?
491	Szirmai et al., 2002, case TI		63	M	I	–	+	R	?	?
492	Szirmai et al., 2002, case UF		55	F	H	+	+	L	?	?
493	Szirmai et al., 2002, case OJ		45	M	I	+	+	R	?	?
494	Szirmai et al., 2002, case TA		64	M	I	–	+	L	?	?
495	Tülay et al., 2002, case 2	2	65	M	H	–	–	L	–	+
496	Annoni et al., 2003, case 1	**9**	**73**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
497	Annoni et al., 2003, case 2		22	M	I	+	+	L	–	+
498	Annoni et al., 2003, case 3		**53**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
499	Annoni et al., 2003, case 4		50	M	I	+	+	L	–	+
500	Annoni et al., 2003, case 5		**65**	**F**	**I**	**+**	**+**	**R**	**+**	**+**
501	Annoni et al., 2003, case 6		**59**	**M**	**I**	**+**	**+**	**R**	**+**	**+**

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Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
502	Annoni et al., 2003, case 7		52	M	I	+	+	R	–	+
503	Annoni et al., 2003, case 8		63	M	I	+	+	R	–	+
504	Annoni et al., 2003, case 9		68	F	I	+	+	R	–	+
505	Bjornstad et al., 2003	1	82	M	I	+	–	Bi	–	?
506	Dietl et al., 2003	1	73	F	H	+	–	L	–	?
507	Jung et al., 2003	1	70	M	H	–	–	R	–	+
508	Miller et al., 2003	1	33	M	I	–	+	Bi	?	?
509	Radanovic et al., 2003, 2004, case 1	6	64	F	I	+	+	L	–	+
510	Radanovic et al., 2003, 2004, case 2		22	F	I	–	+	L	–	+
511	Radanovic et al., 2003, 2004, case 3		27	M	H	+	+	L	–	+
512	Radanovic et al., 2003, 2004, case 4		65	M	I	th +	+	R	–	+
513	Radanovic et al., 2003, 2004, case 5		**49**	**M**	**H**	**+**	**+**	**R**	**+**	**+**
514	Radanovic et al., 2003, case 6		65	M	H	–	+	R	–	+
515	Radanovic and Scaff, 2003, case 10	16	50	F	H	th +	+	L	–	+
516	Radanovic and Scaff, 2003, case 11		60	M	H	+	+	R	–	+
517	Radanovic and Scaff, 2003, case 12		77	M	H	+	+	L	–	+
518	Radanovic and Scaff, 2003, case 14		73	F	H	th +	+	L	–	+
519	Radanovic and Scaff, 2003, case 15		24	M	H	+	+	L	–	+
520	Radanovic and Scaff, 2003, case 16		73	M	I	th +	+	L	–	+
521	Schott et al., 2003	**1**	**68**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
522	Segal et al., 2003	**1**	**48**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
523	Studer and Baumgartner, 2003	1	55	M	I	–	–	R	–	?
524	Tamamoto et al., 2003	1	67	F	I	+	–	Bi	–	?
525	Van Borsel et al., 2003	1	38	M	I	+	+	L	–	+
526	Vucic et al., 2003	1	43	M	I	–	+	Bi	+	+
527	Van der Werf et al., 2003, case 1	22	22	M	I	–	+	L	+	+
528	Van der Werf et al., 2003, case 2		**31**	**M**	**I**	**+**	**+**	**R**	**+**	**+**
529	Van der Werf et al., 2003, case 3		38	M	I	+	+	L	–	+
530	Van der Werf et al., 2003, case 4		44	F	I	+	+	R	–	–
531	Van der Werf et al., 2003, case 5		**46**	**F**	**I**	**+**	**+**	**L**	**+**	**+**
532	Van der Werf et al., 2003, case 6		47	M	I	–	+	L	+	+
533	Van der Werf et al., 2003, case 7		50	M	I	–	+	L	–	+
534	Van der Werf et al., 2003, case 8		54	F	I	–	+	Bi	–	+
535	Van der Werf et al., 2003, case 9		54	M	I	+	+	Bi	–	+
536	Van der Werf et al., 2003, case 10		54	M	I	+	+	Bi	–	+
537	Van der Werf et al., 2003, case 12		57	M	I	+	+	L	–	+
538	Van der Werf et al., 2003, case 13		58	M	I	–	+	Bi	–	+
539	Van der Werf et al., 2003, case 14		60	M	I	+	+	R	–	+
540	Van der Werf et al., 2003, case 15		66	F	I	–	+	R	–	–
541	Van der Werf et al., 2003, case 16		66	F	I	–	+	Bi	+	–
542	Van der Werf et al., 2003, case 17		**68**	**F**	**I**	**+**	**+**	**R**	**+**	**+**
543	Van der Werf et al., 2003, case 18		71	M	I	–	+	Bi	?	+
544	Van der Werf et al., 2003, case 19		72	M	I	–	+	L	+	+
545	Van der Werf et al., 2003, case 20		75	F	I	–	+	R	–	–
546	Van der Werf et al., 2003, case 21		82	F	I	–	+	L	+	+
547	Van der Werf et al., 2003, case 22		83	F	I	–	+	L	+	–
548	Walla et al., 2003	**1**	**57**	**M**	**I**	**+**	**+**	**Bi**	**+**	**+**
549	Ances et al., 2004	1	35	F	I	+	–	Bi	–	?
550	Ameridou et al., 2004	1	47	F	I	–	–	Bi	–	?
551	Barrett et al., 2004	1	27	F	H	+	–	L	–	?
552	Cavaco et al., 2004, case 5	10	57	M	I	+	+	R	+	?
553	Hermann et al., 2004	1	47	F	I	+	–	L	–	?
554	Nagaratnam et al., 2004, case 1	2	59	M	I	+	–	R	–	?
555	Nagaratnam et al., 2004, case 2		73	F	I	+	–	R	–	?
556	Nys et al., 2004	1	46	M	I	+	+	Bi	–	–

Appendix 1. (*continued*)

Case	Reference	*n*	Age	M/F	Aetiology (H/I)	Focal thalamic lesion (CT/MRI)	Formal assessment of neurocognitive functions	Lesion	Clinical data assessed in the lesion phase	Dextral
557	Predescu et al., 2004	1	38	M	I	–	–	Bi	–	?
558	Rai et al., 2004	1	65	M	I	+	+	L	+	?
559	Sibon and Burbaud, 2004	1	70	M	H	+	–	R	–	?
560	Annoni et al., 2005, case 2	2	71	M	I	+	+	R	–	–
561	Bellebaum et al., 2005, case 1	13	54.2	M	I	+	+	R	–	?
562	Bellebaum et al., 2005, case 2		54.2	M	I	+	+	R	–	?
563	Bellebaum et al., 2005, case 3		54.2	M	I	+	+	L	–	?
564	Bellebaum et al., 2005, case 4		54.2	M	I	+	+	L	–	?
565	Bellebaum et al., 2005, case 5		54.2	M	I	+	+	R	–	?
566	Bellebaum et al., 2005, case 6		54.2	M	I	–	+	L	–	?
567	Bellebaum et al., 2005, case 7		54.2	M	I	+	+	Bi	–	?
568	Bellebaum et al., 2005, case 8		54.2	F	I	+	+	L	–	?
569	Bellebaum et al., 2005, case 9		54.2	F	I	+	+	R	–	?
570	Bellebaum et al., 2005, case 10		54.2	F	I	+	+	R	–	?
571	Bellebaum et al., 2005, case 11		54.2	F	I	+	+	L	–	?
572	Bellebaum et al., 2005, case 12		54.2	F	I	+	+	Bi	–	?
573	Bellebaum et al., 2005, case 13		54.2	F	I	+	+	L	+	?
574	Bezerra et al., 2005, case 1	2	18	F	I	–	–	Bi	–	?
575	Bezerra et al., 2005, case 2		49	F	I	th +	–	Bi	–	?
576	Kishiyama et al., 2005	1	40	M	I	–	+	Bi	–	+
577	Lee et al., 2005	1	76	F	I	+	–	R	–	+
578	**Levin et al., 2005**	**1**	**56**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
579	**Linek et al., 2005**	**1**	**52**	**M**	**I**	**+**	**+**	**L**	**+**	**+**
580	Perren et al., 2005, case 1	12	31	M	I	–	+	L	?	?
581	Perren et al., 2005, case 2		65	F	I	–	+	Bi	?	?
582	Perren et al., 2005, case 3		69	F	I	–	+	L	?	?
583	Perren et al., 2005, case 4		48	M	I	+	+	R	?	?
584	Perren et al., 2005, case 5		35	M	I	–	+	R	?	?
585	Perren et al., 2005, case 6		48	F	I	–	+	R	?	?
586	Perren et al., 2005, case 7		68	M	I	–	+	Bi	?	?
587	Perren et al., 2005, case 8		65	F	I	+	+	R	?	?
588	Perren et al., 2005, case 9		78	F	I	+	+	L	?	?
589	Perren et al., 2005, case 10		64	F	I	–	+	R	?	?
590	Perren et al., 2005, case 11		68	M	I	–	+	Bi	?	?
591	Perren et al., 2005, case 12		65	M	I	–	+	R	?	?
592	Woerner et al., 2005	1	71	M	I	–	–	Bi	–	+
593	Blitshteyn et al., 2005	1	82	F	I	+	–	L	–	?
594	De Witte et al., 2006	1	78	F	I	–	+	Bi	+	+
595	Giannopoulos et al., 2005	1	63	M	I	+	–	Bi	–	?
596	Gold and Squire, 2006, case MG	3	55	M	I	+	+	Bi	?	+
597	Mutarelli et al., 2006	1	63	M	I	+	+	Bi	?	+
598	Özeren et al., 2006, case 1	3	60	F	H	–	+	L	+	+
599	Özeren et al., 2006, case 2		65	F	H	–	–	L	–	+
600	Özeren et al., 2006, case 3		65	F	H	–	–	L	–	+
601	Yoshita and Yamada, 2006, case 2	2	75	M	H	+	–	R	–	?
602	Josseaume et al., 2007	1	49	M	I	+	+	Bi	–	+
603	**Kuljic-Obradovic et al., 2007**	**1**	**60**	**M**	**H**	**+**	**+**	**Bi**	**+**	**+**
604	Kumral et al., 2007, case 1	5	69	M	I	+	+	Bi		?
605	Kumral et al., 2007, case 2		63	F	I	+	+	Bi	?	?
606	Kumral et al., 2007, case 3		54	M	I	+	+	Bi	?	?
607	Kumral et al., 2007, case 4		53	F	I	th +	+	L	?	?
608	Kumral et al., 2007, case 5		76	F	I	+	+	L	?	?
609	Mondon et al., 2007	1	48	F	I	+	–	Bi	–	?
610	Park et al., 2007	1	70	M	I	–	+	Bi	+	+
611	Stenset et al., 2007	1	67	F	I	+	+	L	–	+
612	Myint et al., 2008	1	63	F	I	+	–	Bi	–	+
613	Shim et al., 2008, case 1	4	62.7	M	I	+	+	L	–	+
614	Shim et al., 2008, case 2		62.7	M	I	+	+	L	–	+
615	Shim et al., 2008, case 3		62.7	M	I	+	+	L	–	+
616	Shim et al., 2008, case 4		62.7	F	I	+	+	L	–	+
617	Azabou et al., 2009	1	74	F		–	–	L	–	+
618	Hampstead and Koffler, 2009	1	49	F	I	–	+	Bi	+	+

n = Number of cases, M = male, F = female, H = haemorrhage, I = infarction, L = left thalamic lesion, R = right thalamic lesion, Bi = bilateral thalamic lesion, th + = thalamic lesion with involvement of the internal capsule, + = present, – = absent, ? = no info available, cases printed in bold = reliable case-reports, case 399 = Engelborghs et al. + unpublished case, case 561–573: 54.2 = mean age, case 613–616: 62.7 = mean age.

Appendix 2.
Summary of the 42 reliable vascular thalamic cases: demographic, neurolinguistic, neurocognitive and neuroradiological data

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[1]	Alexander and LoVerme, 1980, case 1	73/M	Assessment at 6 weeks postonset: slightly dysarthric, fluent speech with normal comprehension, normal repetition, decreased naming (word finding pauses, circumlocutions, semantic paraphasias), normal reading and mildly impaired writing; mild visual attention problems, impaired memory in both verbal and nonverbal skills, normal praxis but mildly impaired construction, normal calculation, perseveration was not prominent in any test, mildly impaired affect	Haematoma in the left posterior thalamus
[2]	Alexander and LoVerme, 1980, case 2	62/F	Assessment between 3 weeks and 3 months postonset: fluent speech with normal articulation, normal repetition, normal comprehension, moderately impaired naming; normal reading and writing; normal construction, normal calculation, normal praxis, normal visual attention, moderately impaired visual and verbal memory, normal affect	Left thalamic haemorrhage
[3]	Alexander and LoVerme, 1980, case 3	72/M	Assessment at 12 weeks postonset: fluent speech with normal comprehension, normal repetition, mildly impaired naming (paraphasias), normal reading, moderately impaired writing; mildly impaired visual attention, mildly impaired construction, no further praxis problems, normal calculation, normal memory, no perseverations and mildly impaired affect	Left thalamic haemorrhage
[41	Alexander and LoVerme, 1980, case 4	64/M	Assessment at 3 weeks postonset: fluent, well-articulated speech with normal comprehension, normal repetition and mildly impaired naming, reading and writing (no paraphasias); normal calculation, mildly impaired construction, no further praxis problems, normal visual attention, moderately impaired memory and mildly impaired affect	Left thalamic haemorrhage
[6]	Alexander and LoVerme, 1980, case 7	69/M	Assessment at 5 weeks postonset: slightly dysarthric but fluent speech with normal comprehension, normal repetition, moderately impaired naming (paraphasias), mildly impaired reading and severely impaired writing, severely impaired construction and calculation, mildy impaired praxis, severely impaired memory and visual attention (right neglect), moderately impaired affect and the presence of perseverations	Left thalamic haemorrhage

Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[7]	Alexander and LoVerme, 1980, case 8	57/F	Assessment at 5 weeks postonset: fluent speech with word finding pauses, verbal and neologistic paraphasias; good auditory and reading comprehension except for more complex material; poor naming with paraphasias and neologisms; normal repetition, reading aloud with paraphasic errors; mildly impaired writing; normal praxis although some simplified drawings; markedly deficient calculation; good visual attention, no major deficits on memory testing; flattened affect	Left thalamic haemorrhage in the posterior region
[8]	Alexander and LoVerme, 1980, case 9	41/M	Assessment at 5 weeks postonset: slightly dysarthric but fluent speech with moderately impaired comprehension, mildly impaired repetition, moderately impaired naming, normal reading and severely impaired writing, mild constructional and mild praxic problems with mild visual attentional problems, moderately impaired memory, mild disturbances on the affective level	Left thalamic haemorrhage in the posterior region
[10]	Cohen et al., 1980	62/M	Assessment at 4 and 6 weeks postonset: alert, oriented, cooperative patient, fluent speech with little difficulty in auditory comprehension and verbal expression (phonemic paraphasias) and mild word-finding difficulty, auditory comprehension deteriorated with increasing length and complexity (Token Test), poor comprehension of complex written material, normal oral reading, normal repetition, numerous spelling errors in writing to dictation and spontaneous writing, mildly impaired naming (declined as a function of word frequency), normal operation of simple arithmetic operations; normal visual attention	Left thalamic infarction in the anterior region
[12]	Archer et al., 1981	57/M	Assessment at 8 weeks postonset: normal articulation, normal fluency, normal repetition, mildly impaired auditory comprehension, moderate anomia, mild impairment of attention, severely impaired verbal and visual memory and normal constructional abilities	Infarction in the anterior one half of the left ventro-lateral thalamus + PLIC
[42]	Guberman and Stuss, 1983, case 1	54/M	Assessment at 3 weeks postonset: hypophonic, monotonous fluent speech, minimal impaired repetition and comprehension, normal reading and writing, moderately impaired naming, severely impaired anterograde and retrograde verbal and visual memory, moderately impaired VIQ (PIQ – unable), Stroop test and TMT unable to do; behaviour characterised by apathy, aspontaneity, occasional impulsive aggressive outbursts, flattened affect and anosognosia	Small hypodense area in both medial thalami

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Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[45]	Gorelick et al., 1984	70/F	Assessment at almost 3 weeks postonset: fluent, well-articulated soft speech with normal intonation and grammatical form; mild to moderate auditory comprehension deficits, manifest word retrieval problems; verbal output characterised by verbal paraphasias, jargon and neologisms; intact repetition; severely impaired reading and writing skills	Nonenhancing lucency in the left VA and VL thalamus + ALIC + (slight extension to PG)
[68]	Graff-Radford et al., 1985, case 6	19/M	Assessment at 3 weeks postonset: normal repetition, normal naming, normal temporal orientation, normal VIQ, mildly impaired PIQ, normal visual/verbal memory, deficient concentration, normal facial recognition/line orientation	Right posterolateral thalamic infarction
[71]	Graff-Radford et al., 1985, case 9	60/M	Assessment at 14 weeks postonset: normal reading, normal temporal orientation, normal mental control, normal verbal memory scores, deficient visual memory, mildly impaired IQ-scores, normal facial recognition and normal line judgment	Left posterolateral thalamic infarct + associated posterior cerebral infarct
[73]	Graff-Radford et al., 1985, case 11	75/M	Assessment at 12 weeks postonset: deficient naming, normal repetition, normal reading, temporal desorientation, deficient verbal and visual memory, moderately impaired IQ-scores, normal mental control, impaired facial recognition and line orientation	Left anterolateral thalamic infarct
[74]	Graff-Radford et al., 1985, case 12	66/F	Assessment at 3 weeks postonset: deficient naming, normal repetition, temporal desorientation, deficient visual memory and impaired facial recognition	Left anterolateral thalamic infarct
[76]	Graff-Radford et al., 1985, case 21	47/M	Assessment at 4 weeks postonset: normal naming and normal repetition; normal temporal orientation, normal concentration, normal IQ-scores, severely impaired verbal and visual memory, deficient constructional praxis, impaired facial recognition and line orientation	Lesion in the left lateral thalamus + the posterior IC
[100]	Cappa et al., 1986, case 1	53/M	Assessment at 3 weeks postonset: good description of an event, minimal impairment of naming, normal automatic sequencing, normal auditory word comprehension, normal Token Test, normal repetition, normal written expression, normal written word comprehension, minimal impaired written sentence comprehension, normal reading aloud and writing on dictation	Left haemorrhagic area involving the posterior thalamus and the PLIC
[101]	Cappa et al., 1986, case 2	49/M	Assessment at 4 weeks postonset: good description of an event, minimal impairment of naming, normal automatic sequencing, normal auditory word comprehension, minimal impaired auditory sentence comprehension, normal Token Test, normal repetition of letters–syllables–words–sentences, minimal impaired repetition of nonwords, normal spontaneous writing, normal reading comprehension and reading aloud, minimal impaired writing	Hyperdense area involving the left posterior thalamus and the PLIC

Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[103]	Cappa et al., 1986, case 4	74/M	Assessment at 4 weeks postonset: good description of an event, minimal impairment of naming, normal automatic sequencing, normal auditory word comprehension, minimally impaired comprehension of semantically related words and sentences, mildly impaired Token Test, normal repetition of words and sentences, minimal impairment of repetition of letters and syllables and moderately impaired repetition of nonwords, normal reading aloud and minimally impaired written comprehension of semantically related words and sentences	Hyperdense area involving the left posterior thalamus and the PLIC
[104]	Cappa et al., 1986, case 5	65/M	Assessment at 4 weeks postonset: good description of an event, mildly impaired naming, normal auditory comprehension of words and sentences sentences and non-words, mildly impaired comprehension of semantically related words, normal repetition of letters–words–sentences are mildly impaired repetition of syllables, normal reading aloud, normal written comprehension of words–sentences, minimal impairment of semantically related words (see Table 1)	Hyperdense area involving the left posterior thalamus and PLIC
[114]	Mori et al., 1986	41/M	Assessment at 6 weeks postonset: with regard to language function: normal repetition, normal comprehension, normal reading, minimal impairment of naming, mildly impaired writing, normal IQ-scores, severely impaired verbal memory, normal visual memory, normal calculation, normal WCST-score, mildly impaired word fluency	Hypodense zone in the left anterior thalamus
[132]	Fasanaro et al., 1987	59/M	Assessment at 3 weeks postonset: aphasia profile consistent with a transcortical sensory aphasia: fluent, dysprosodic speech with verbal paraphasias and stereo-typies, normal automatic sequencing, moderately impaired naming, severely impaired auditory/written comprehension, normal repetition, severely impaired reading aloud of letters–words–neologisms and sentences, severely impaired writing; constructional apraxia and deficient memory	Paramedian infarction of the left (medial) thalamus
[157]	Fensore et al., 1988, case 1	67/M	Assessment at 3 weeks postonset: fluent well-articulated speech, minimally impaired auditory comprehension for words and sentences, normal naming, minimal impairment of repetition of low-probability sentences, minimal impairment of reading comprehension and reading, normal writing; mildly impaired attention, no visuo-spatial deficits, no apraxias, no agnosias, moderate verbal memory impairment of the anterograde type, good memory for faces, good anterograde/retrograde visual memory, mildly impaired calculation, good left/right identification	Infarction in the anterior left thalamus + PLIC

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Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[202]	Robin and Schienberg, 1990, T2	71/F	Assessment at 4 weeks postonset: fluent, well-articulated, prosodic, hypophonic spontaneous speech with verbal paraphasias and neologisms, moderately impaired auditory comprehension, moderately impaired naming (with neologisms, jargon, verbal paraphasias), moderately impaired repetition, normal reading aloud, no oral apraxia	Infarction in the left anterior thalamus + PLIC
[279]	Ibayashi et al., 1992, case 1	44/M	Assessment at 3 weeks postonset: fluent speech with mildly impaired comprehension and moderately impaired naming and word finding (paraphasias), no perseverations, normal repetition	Haemorrhage in the central and posterior region of the left thalamus
[282]	Ibayashi et al., 1992, case 13	66/M	Assessment at 4 weeks postonset: hypophonic, fluent speech with mildly disturbed comprehension, normal repetition, moderately impaired naming (word finding) with paraphasias and no perseveration	Haemorrhage in the lateral, posterior region of the left thalamus
[284]	Ibayashi et al., 1992, case 19	51/M	Assessment at 3, 5 weeks postonset: mild hypophonic, fluent speech with moderately impairment of comprehension, normal repetition, moderately impaired word finding (paraphasias) with no perseverations	Haemorrhage in the central, lateral and posterior region of the left thalamus
[285]	Ibayashi et al., 1992, case 21	65/F	Assessment at 4 weeks postonset: normal fluent speech with normal comprehension, normal repetition, mildly impaired naming and word finding, no perseverations	Haemorrhage in the posterior region of the left thalamus
[286]	Ibayashi et al., 1992, case 22	65/F	Assessment at 4 weeks postonset: normal fluent speech with normal repetition, moderately impaired comprehension, severely impaired naming (paraphasias, perseverations)	Haemorrhage in the posterior region of the left thalamus
[288]	Maeshima et al., 1992	60/F	Assessment at 3 weeks postonset: markedly reduced spontaneous but fluent speech, severely impaired auditory word and sentence comprehension, mildly impaired written word comprehension, severely impaired written sentence comprehension, mildly impaired repetition, severe disturbance of naming and word finding (semantic paraphasias, neologisms), normal reading aloud, severely disturbed writing; no oral or ideomotor apraxia and no unilateral spatial neglect, normal orientation	Infarction in the ventral region of the left thalamus
[327]	Clarke et al., 1994	54/F	Assessment at 16 weeks postonset: good language functions (normal production, comprehension, repetition and naming), no apraxias, good visual gnosis and good visuoconstructive abilities, poor verbal and nonverbal fluency, deficient scores on Stroop and mildly disturbed WCST-score, normal sustained attention, normal reaction, normal orientation, severely disturbed verbal memory, normal nonverbal IQ-score; personality change: less concerned, lack of motivation, difficulties in initiating tasks	Infarction in the anterior part of the left thalamus

Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[344]	Haut et al., 1995	40/F	Assessment at 6 weeks postonset: normal naming, normal verbal category fluency, deficient temporal orientation, mild deficits with visual problem solving and verbal abstract reasoning, severe anterograde verbal/visual amnesia, normal WCST-score, inappropriate affect, limited insight	Bithalamic infarction in the anteromedial region
[345]	Luchelli et al., 1995; Luchelli and De Renzi, 1992, case GR	67/M	Assessment at 8 weeks postonset: remarkable hypo-phonia, psychometric free of any aphasic disorder, mildly disturbed literal fluency, normal IQ-scores, severely disturbed anterograde verbal memory, minimal impairment for visual memory, deficient retrograde autobiographical memory, no visual attention disorder, normal facial recognition; personality changes: apathy, empty mind,…	Ischaemic lesion in the region of the left anterior thalamus and IC
[349]	Sodeyama et al., 1995	57/M	Assessment at 8 weeks postonset: fluent speech with normal prosody and grammatical form, normal or minimal impairment on auditory comprehension, naming, writing, reading, calculation) + normal repetition, normal attention, moderately impaired verbal memory, mild visual memory impairment, normal IQ-scores	Left thalamic infarction
[354]	Kumar et al., 1996	55/M	Assessment at 4 weeks postonset: non-fluent speech, description of a picture was impossible, severely impaired auditory and written comprehension, severely impaired repetition, unability to read and write, severely impaired naming (paraphasias, perseverations)	Haemorrhage in the left thalamus
[359]	Crosson et al., 1997	46/M	Assessment at 8 weeks postonset: language skills within normal limits, slightly reduced verbal fluency (neurocognitive assessment only performed in the late phase)	Haemorrhage in the posterior region of left thalamus + PLIC
[397]	Barrett et al., 2000, case KH	52/F	Assessment at 4 weeks postonset: all aspects of speech and language were normal except for verbal fluency, verbal amnesia with normal recognition, no spatial neglect in near extrapersonal space, spatial neglect in far extrapersonal space, normal calculation, normal praxis, normal left–right orientation	Left thalamic infarction
[513]	Radanovic et al., 2003, 2004, case 5	49/M	Assessment at 12 weeks postonset: fluent spontaneous speech, minimally impaired repetition, normal auditory comprehension score, moderately impaired score on the TT, moderate anomia on the BNT, writing and reading not testable, normal animal fluency, severe visual discrimination, severely disturbed visual memory, severely disturbed TMT and WCST	Right thalamic haemorrhage

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Appendix 2. (*continued*)

Case	Reference	Age/sex	Neurocognitive symptoms in the lesion phase	Lesion localisation
[521]	Schott et al., 2003	68/M	Assessment at 4 weeks postonset: fluent speech with normal verbal comprehension, normal reading and minimal impaired naming (no evidence for a dysphasic syndrome), normal calculation, normal intelligence, normal visual memory, severely disturbed anterograde verbal memory	Discrete infarction in the left thalamus
[522]	Segal et al., 2003	48/M	Assessment at 16 weeks postonset: halting speech with frequent hesitations, normal repetition, normal reading, normal written comprehension, mildly impaired auditory comprehension, severely disturbed naming, poor verbal fluency	Left thalamic infarction
[578]	Levin et al., 2005	56/M	Assessment at 4 weeks postonset: fluent speech, normal repetition, normal comprehension, normal reading, normal writing, moderately impaired naming (mostly semantic errors and visual errors), deficient constructional praxis, severely impaired verbal and performal IQ-scores, severely impaired verbal memory, moderately impaired WCST	Ischaemic lesion in the left anterior thalamus
[603]	Kuljic-Obradovic et al., 2007	60/M	Assessment at 4 weeks postonset: fluent language with normal repetition, normal comprehension and moderately impaired naming, poor category and letter verbal fluency, mildly impaired visuo-construction, severely impaired orientation, severely impaired concentration, severely impaired anterograde verbal and visual memory, severe retrograde amnesia, severely impaired executive functions (WCST) with slowing of mental processing speed, loss of cognitive flexibility, loss of initiative, lack of insight, lack of interest and no concern about the future	Bilateral thalamic haemorrhage in the medial region

M = male, F = female, IC = internal capsule, PLIC = posterior limb of the internal capsule, ALIC = anterior limb of the internal capsule, PG = pallidal globe, DM = dorsomedial nucleus, VA = ventral anterior part, VL = ventral lateral part, PaVWM = paraventricular white matter, TT = Token Test, BNT = Boston Naming Test, BDAE = Boston Diagnostic Aphasia Examination, MMSE = Mini Mental State Examination, TMT = Trail Making Test, WMS = Wechsler Memory Scale, WCST = Wisconsin Card Sorting Test, VIQ = verbal IQ, PIQ = performal IQ.

Appendix 3.
Analysis of the neurolinguistic symptoms of the 42 reliable vascular thalamic cases

Case	Reference	Age/sex	Aphasic symptoms						Dysarthric symptoms	Dysprosodia	Additional information	Lesion site
			Fluency	Comprehension	Repetition	Naming	Reading	Writing				
[1]	Alexander and LoVerme, 1980, case 1	73/M	0	0	0	1	0	1	1	?	Word finding problems for lower-frequency items, articulation deficits	Resolving haematoma in the left posterior thalamus
[2]	Alexander and LoVerme, 1980, case 2	62/F	0	0	0	2	0	0	?	?		Left thalamic haemorrhage
[3]	Alexander and LoVerme, 1980, case 3	72/M	0	0	0	1	0	2	0	?	Word finding problems characterised by paraphasias	Left thalamic haemorrhage
[4]	Alexander and LoVerme, 1980, case 4	64/M	0	0	0	1	1	1	?	?		Left thalamic haemorrhage
[6]	Alexander and LoVerme, 1980, case 7	69/M	0	0	0	2	1	3	1	?	Word finding problems characterised by paraphasias, articulation deficits	Left thalamic haemorrhage
[7]	Alexander and LoVerme, 1980, case 8	57/F	0	1	0	2	1	1	0	?	Slightly dysarthric speech which was normal at 3 months post-onset	Left thalamic haemorrhage in the posterior region
[8]	Alexander and LoVerme, 1980, case 9	41/M	0	2	1	2	0	3	1	?	Word finding problems characterised by paraphasias, articulation deficits	Left thalamic haemorrhage in the posterior region
[10]	Cohen et al., 1980	62/M	0	1	0	1	0	2	?	?		Left thalamic infarction in the anterior region
[12]	Archer et al., 1981	57/M	0	I	0	2	?	?	?	?		Infarction in the anterior one half of the left ventrolateral thalamus + PLIC
[42]	Guberman and Stuss, 1983, case 1	54/M	0	1	1	2	0	0	1	1	Low volume, monotonous speech reduced spontaneous speech	Small hypodense area in both medial thalami

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Appendix 3. (*continued*)

Case	Reference	Age/ sex	Aphasic symptoms						Dysarthric symptoms	Dysprosodia	Additional information	Lesion site
			Fluency	Comprehension	Repetition	Naming	Reading	Writing				
[45]	Gorelick et al., 1984	70/F	0	1	0	3	3	3	0	0	Verbal output characterised by semantic paraphasias, extended jargon and neologisms	Nonenhancing lucency in the left ventral anterior and ventral lateral thalamus
[68]	Graff-Radford et al., 1985, case 6	19/M	?	?	?	0	0	?	?	?		Right posterolateral thalamic infarction (=geniculo thalamic artery territory)
[71]	Graff-Radford et al., 1985, case 9	60/M	?	?	?	?	0	?	?	?		Left posterolateral thalamic infarct + associated posterior cerebral infarct
[73]	Graff-Radford et al., 1985, case 11	75/M	?	?	0	2	0	?	?	?		Left anterolateral thalamic infarct (lesion in the tuberothalamic artery)
[74]	Graff-Radford et al., 1985, case 12	66/F	?	?	0	2	?	?	?	?		Left anterolateral thalamic infarct (lesion in the tuberothalamic artery)
[76]	Graff-Radford et al., 1985, case 21	47/M	?	?	0	0	?	?	?	?		Lesion in the left lateral thalamus + the posterior IC
[100]	Cappa et al., 1986, case 1	53/M	0	0	0	0	0	0	?	?	Mild impairment of written sentence comprehension	Left hemorrhagic area involving the posterior thalamus and the PLIC
[101]	Cappa et al., 1986, case 2	49/M	0	0	0	0	0	2	?	?	Mild impairment of auditory sentence comprehension	Hyperdense area involving the left posterior thalamus and the PLIC
[103]	Cappa et al., 1986, case 4	74/M	0	0	1	0	0	?	?	?		Hyperdense area involving the left posterior thalamus and the PLIC
[104]	Cappa et al., 1986, case 5	65/M	0	0	0	1	0	?	?	?		Hyperdense area involving the left posterior thalamus and the PLIC
[114]	Mori et al., 1986	41/M	?	0	0	0	0	1	?	?		Hypodense zone in left anterior thalamus
[132]	Fasanaro et al., 1987	59/M	0	3	0	2	3	3	?	2		Ischaemic area confined to the left capsular thalamic region
[157]	Fensore et al., 1988, case 1	67/M	0	0	0	0	0	0	?	?		Paramedian infarction of the left (medial) thalamus

[202]	Robin and Schienberg, 1990, T2	71/F	0	2	3	2	2	?	1	0	Intermittent hypophonia, fluent speech	Infarction in the left anterior thalamus + PLIC
[279]	Ibayashi et al., 1992, case 1	44/M	0	1	0	1	?	?	?	?	Naming characterised by paraphasias normal vocal volume	Haemorrhage in the central and posterior region of the left thalamus
[282]	Ibayashi et al., 1992, case 13	66/M	0	1	0	2	?	?	1		Mild hypophonic speech naming characterised by paraphasias	Haemorrhage in the lateral and posterior region of the left thalamus
[284]	Ibayashi et al., 1992, case 19	51/M	0	2	0	2	?	?	1	?	Mild hypophonic speech naming characterised by paraphasias	Haemorrhage in the central, lateral and posterior region of the left thalamus
[285]	Ibayashi et al., 1992, case 21	65/F	0	0	0	1	?	?	?	?		Haemorrhage in the posterior region of the left thalamus
[286]	Ibayashi et al., 1992, case 22	65/F	0	2	0	3	?	?	?	?	Naming characterised by perseverations and paraphasias	Haemorrhage in the posterior region of the left thalamus
[288]	Maeshima et al., 1992	60/F	0	3	1	3	0	3	?	?	Naming characterised by semantic paraphasias, neologisms, reduced spontaneous speech	Infarction in the ventral region of the left thalamus {occlusion of the posterior communicating artery
[327]	Clarke et al., 1994	54/F	?	?	?	2	?	?	?	?		Infarction in the anterior part of the left thalamus
[344]	Haut et al., 1995	40/F	?	?	?	0	?	?	?	?		Bithalamic infarction in the antero-medial region (=paramedian artery)
[345]	Luchelli et al., 1995; Luchelli and De Renzi, 1992, case GR	67/M	0	?	?	0	?	?	1	?	Selective proper name anomia	Ischaemic lesion in the region of the left anterior thalamus and IC
[349]	Sodeyama et al., 1995	57/M	0	0	0	0	0	0	0	0	Fluent speech with normal prosody and grammatical form	Left thalamic infarction
[354]	Kumar et al., 1996	55/M	2	3	3	3	3	3	3	?	Diagnosed as global aphasia	Haemorrhage in the left thalamus
[359]	Crosson et al., 1997	46/M	0	0	0	1	0	0	?	?	Category-specific naming deficit for medical terms	Small haemorrhage in the posterior region of the left thalamus + PLIC
[397]	Barrett et al., 2000, case KH	52/F	0	0	0	0	0	0	?	?		Left thalamic infarction in the paramedian thalamic artery territory
[513]	Radanovic et al., 2003, 2004, case 5	49/M	0	0	0	2	?	?	?	?		Right thalamic haemorrhage
[521]	Schott et al., 2003	68/M	0	0	?	0	0	?	?	?	Fluent expression	Discrete infarction in the left thalamus
[522]	Segal et al., 2003	48/M	2	1	0	3	0	?	?	?	Halting speech with frequent hesitations	Left thalamic infarction

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Appendix 3. (*continued*)

Case	Reference	Age/ sex	Aphasic symptoms						Dysarthric symptoms	Dysprosodia	Additional information	Lesion site
			Fluency	Comprehension	Repetition	Naming	Reading	Writing				
[578]	Levin et al., 2005	56/M	0	0	0	2	0	0	?	?	Fluent speech, category specific dysnomia	Ischaemic lesion in the left anterior thalamus
[603]	Kuljic-Obradovic et al., 2007	60/M	0	0	0	2	?	?	?	?		Bilateral thalamic haemorrhage situated in the medial region

M = male, F = female, 0 = normal or minimal impairment, 1 = mild impairment, 2 = moderate impairment, 3 = severe impairment, ? = no information, NA = not assessed, IC = internal capsule, PLIC = posterior limb of the internal capsule, ALIC = anterior limb of the internal capsule, DM = dorsomedial nucleus, IML = internal medullar lamina, PaVWM = paraventricular white matter.

Appendix 4.
Analysis of the neurocognitive symptoms of the 42 reliable vascular thalamic cases

					praxis			gnosis										
case	reference	age/ sex	visual attention	oral	constructional	ideational	ideomotor	visual	nosognosia	calculia	orientation	global intellectual functioning	concentration	memory	executive functions	behaviour / mood	additional info	lesion site
[1]	Alexander et al., 1980 case 1	73/M	1	0	1	0	0	?	?	0	?	?	?	2	?	1	impaired verbal and nonverbal memory; mildly impaired affect	resolving haematoma in the left posterior thalamus
[2]	Alexander et al., 1980 case 2	62/F	0	0	0	0	0	?	?	0	?	?	?	2	?	0	impaired memory in verbal and nonverbal skills	left thalamic haemorrhage
[3]	Alexander et al., 1980 case 3	72/M	1	0	1	0	0	?	?	0	?	?	?	0	?	1	mildly impaired affect	left thalamic haemorrhage
[4]	Alexander et al., 1980 case 4	64/M	0	0	1	0	0	?	?	0	?	?	?	2	?	1	impaired verbal and nonverbal memory; mildly impaired affect	left thalamic haemorrhage
[6]	Alexander et al., 1980 case 7	69/M	3	0	3	1	1	?	?	3	?	?	?	3	?	2	impaired memory in verbal and nonverbal skills	left thalamic haemorrhage
[7]	Alexander et al., 1980 case 8	57/F	0	0	1	0	0	?	?	3	?	?	?	0	?	1	behaviour characterised by flattened affect	left thalamic haemorrhage in the posterior region
[8]	Alexander et al., 1980 case 9	41/M	1	0	1	1	1	?	?	?	?	?	?	2	?	1	mild disturbances on the affective level	left thalamic haemorrhage in the posterior region
[10]	Cohen et al., 1980	62/M	0	?	?	?	?	?	?	0	0	?	?	?	?	?		left thalamic infarction in the anterior region
[12]	Archer et al., 1981	57/M	?	?	0	?	?	?	?	?	?	?	1	3	?	?	severely impaired verbal and visual memory	infarction in anterior half of the left ventrolateral thalamus + PLIC
[42]	Guberman et al., 1983 case 1	54/M	0	0	0	0	0	?	3	1	2	2	2	3	3	3	severely disturbed verbal fluency behaviour characterised by apathy, little initiative, aspontaneity, flattened affect,…	small hypodense area in both medial thalami

					praxis			gnosis										
case	reference	age/ sex	visual attention	oral	constructional	ideational	ideomotor	visual	nosognosia	calculia	orientation	global intellectual functioning	concentration	memory	executive functions	behaviour / mood	additional info	lesion site
[45]	Gorelick et al., 1984	70/F	?	?	?	?	?	?	?	?	?	?	?	?	?	?		nonenhancing lucency in the left VA and VL thalamus + ALIC
[68]	Graff-Radford et al., 1985, case 6	19/M	?	?	?	?	?	?	?	?	0	1	2	0	?	?	mildly impaired performal IQ normal facial recognition and line orientation	right posterolateral thalamic infarction
[71]	Graff-Radford et al., 1985, case 9	60/M	?	?	?	?	?	?	?	?	0	1	0	2	?	?		left posterolateral thalamic infarct
[73]	Graff-Radford et al., 1985, case 11	75/M	?	?	?	?	?	?	?	?	2	2	0	2	?	?	impaired facial recognition and line orientation	left anterolateral thalamic infarct
[74]	Graff-Radford et al., 1985, case 12	66/F	?	?	?	?	?	?	?	?	2	?	?	2	?	?		left anterolateral thalamic infarct
[76]	Graff-Radford et al., 1985, case 21	47/M	?	?	2	?	?	?	?	0	?	0	0	3	?	?		lesion in the lateral thalamus and posteri
[100]	Cappa et al., 1986 case 1	53/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		left haemorrhagic area involving the posterior thalamus and PLIC
[101]	Cappa et al., 1986 case 2	49/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		hyperdense area involving the left posterior thalamus and PLIC
[103]	Cappa et al., 1986 case 4	74/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		hyperdense area involving the left posterior thalamus and PLIC
[104]	Cappa et al., 1986 case 5	65/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		hyperdense area involving the left posterior thalamus and PLIC

case	reference	age/ sex	visual attention	praxis: oral	praxis: constructional	praxis: ideational	praxis: ideomotor	gnosis: visual	gnosis: nosognosia	calculia	orientation	global intellectual functioning	concentration	memory	executive functions	behaviour / mood	additional info	lesion site
[114]	Mori et al., 1986	41/M	?	?	?	?	?	?	?	0	?	0	?	3	1	?	mildly disturbed word fluency	hypodense zone in the left anterior thalamus
[132]	Fasanaro et al., 1987	59/M	?	?	2	?	?	?	?	?	?	?	?	2	?	?		ischaemic area confined to the left capsular thalamic region
[157]	Fensore et al., 1988 case 1	67/M	0	0	0	0	0	0	0	1	?	?	1	2	?	?	anterograde verbal memory deficit	paramedian infarction of the left medial thalamus in the paramedian thalamic artery territory
[202]	Robin et al., 1990 T 2	71/F	?	0	?	?	?	?	?	?	?	?	?	?	?	2	inattentive and lethargic behavior during 4 months	infarction in the left anterior thalamus + PLIC
[279]	Ibayashi et al., 1992 case 1	44/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		haemorrhage in the central and posterior region of the left thalamus
[282]	Ibayashi et al., 1992 case 13	66/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		haemorrhage in the lateral, posterior region of the thalamus
[284]	Ibayashi et al., 1992 case 19	51/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		haemorrhage in the central, lateral an posterior region of the left thalamus
[285]	Ibayashi et al., 1992 case 21	65/F	?	?	?	?	?	?	?	?	?	?	?	?	?	?		haemorrhage in the posterior region of the left thalamus
[286]	Ibayashi et al., 1992 case 22	65/F	?	?	?	?	?	?	?	?	?	?	?	?	?	?		haemorrhage in the posterior region of the left thalamus
[288]	Maeshima et al., 1992	60/F	0	0	?	?	0	?	?	?	0	?	?	?	?	2	verbal aspontaneity	infarction in the ventral region of the left thalamus (occlusion of the posterior communicating artery)
[327]	Clarke et al., 1994	54/F	0	0	0	0	0	0	0	?	0	1	0	3	2	2	evolution of global amnesia to a predominantly poor anterograde and retrograde verbal memory	infarction in the anterior part of the left thalamus

case	reference	age/ sex	visual attention	praxis: oral	praxis: constructional	praxis: ideational	praxis: ideomotor	gnosis: visual	gnosis: nosognosia	calculia	orientation	global intellectual functioning	concentration	memory	executive functions	behaviour / mood	additional info	lesion site
[344]	Haut et al., 1995	40/F	?	?	?	?	?	?	2	?	1	1	?	3	0	2	inappropriate affect and limited insight	bithalamic infarction in the antero-medial region (= paramedian artery)
[345]	Luchelli et al., 1995, 1997, case GR	67/M	0	?	?	?	?	?	?	?	?	0	0	3	?	3	severe anterograde and retrograde verbal amnesia, apathy, empty mind, etc	ischaemic lesion in the region of the left anterior thalamus and IC
[349]	Sodeyama et al., 1995	57/M	?	?	?	?	?	?	?	0	?	0	0	2	?	?	anterograde verbal amnesia	left thalamic infarction
[354]	Kumar et al., 1996	55/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		left thalamic haemorrhage
[359]	Crosson et al., 1997	46/M	?	?	?	?	?	?	?	?	?	?	?	?	?	?		small haemorrhage in the posterior region of the left thalamus + PLIC
[397]	Barrett et al., 2000 case KH	52/F	1	0	0	0	0	?	?	?	?	?	?	2	?	?	spatial neglect in far extrapersonal space, deficient verbal fluency	left thalamic infarction (= territory of the paramedian thalamic artery)
[513]	Radanovic et al., 2003, 2004 case 5	49/M	?	?	?	?	?	?	?	?	?	?	?	3	3	?	severely disturbed visual memory	right thalamic haemorrhage in the anterior choroidal + tubero-thalamic artery territory
[521]	Schott et al., 2003	68/M	?	?	?	?	?	?	?	0	?	0	?	3	?	?	normal visual memory, selective anterograde verbal memory deficit	discrete infarction in the left thalamus
[522]	Segal et al., 2003	48/M	?	?	?	?	?	?	?	?	?	?	?	?	2	?	severely impaired verbal fluency	left thalamic infarction
[578]	Levin et al., 2005	56/M	?	?	2	?	?	?	?	?	?	3	?	3	2	?		ischaemic lesion in the left anterior thalamus
[603]	Kuljic-Obradovic et al., 2007	60/M	?	?	1	?	?	?	?	?	3	?	3	3	3	3	impaired categorial and phonemic fluency, marked behaviour alterations (see case summary)	bilateral thalamic haemorrhage situated in the medial region

M = male, F = female, 0 = minimal impairment, 1 = mild impairment, 2 = moderate impairment, 3 = severe impairment, ? = no information, IC = internal capsule, PLIC = posterior limb of the internal capsule, ALIC = anterior limb of the internal capsule, IC = internal capsule, DM = dorso-medial nucleus, PaVM = paraventricular white matter, IML = internal medullar lamina, VA = ventral anterior, VL = ventral lateral, L = left, R = right.

Appendix 5.
Inventarisation of the affective-behavioural description in 75 vascular thalamic cases

Case	Reference	Age/sex	Aetiology (H/I)	Lesion site	Affective-behavioural description (lesion phase)
[1]	Alexander and LoVerme, 1980, case 1	73/M	H	L	Mildy impaired affect
[3]	Alexander and LoVerme, 1980, case 3	72/M	H	L	Mildy impaired affect
[4]	Alexander and LoVerme, 1980, case 4	64/M	H	L	Mildy impaired affect
[6]	Alexander and LoVerme, 1980, case 7	69/M	H	L	Moderately impaired affect
[7]	Alexander and LoVerme, 1980, case 8	57/F	H	L	Mildly impaired affect: flattened affect, little concern about her condition
[8]	Alexander and LoVerme, 1980, case 9	41/M	H	L	Mildy impaired affect
[12]	Archer et al., 1981	57/M	I	L	Verbal aspontaneity
[15]	Lemaire et al., 1981, case 2	63/M	I	L	Behaviour alterations characterised by apathy and boulemia
[42]	Guberman and Stuss, 1983, case 1	54/M	I	Bi	Hypersomnolent, apathy, slowness of thought, little initiative and aspontaneity with occasional impulsive aggressive outbursts and often inappropriate in behaviour and conversation, anosognosia
[46]	Graff-Radford et al., 1984, case 1	67/M	I	L	Verbal aspontaneity, rarely initiating dialogue euphoric behaviour
[48]	Graff-Radford et al., 1984, case 3	75/M	I	L	Verbal aspontaneity, rarely initiating dialogue
[49]	Graff-Radford et al., 1984, case 4	69/F	I	Bi	Personality change: euphoric and delusional ('she falsely believed she was soon going back to being a teacher'), lack of insight
[106]	Gerber and Gudesblatt, 1986, case 1	72/M	I	Bi	Chronic state of marked apathy
[115]	Rondot et al., 1986	45/F	I	Bi	Reduced spontaneous speech, total indifference towards mnestic problems; euphoric behaviour
[135]	Gentilini et al., 1987, case 3	35/M	I	Bi	Behaviour characterised by boulemia, hypersomnia, apathy; irritability
[153]	Waterston et al., 1987, case 2	40/M	I	Bi	A state of akinetic mutism marked by psychomotor retardation, emotional lability, and reduced spontaneous speech
[166]	Stuss et al., 1988, case 1	54/M	I	Bi	Patient remained apathetic and unconcerned, 'under the care of his wife'
[169]	Bruyn, 1989, case 18	65/M	I	L	Reduced spontaneous speech
[170]	Bruyn, 1989, case 19	60/F	H	L	Reduced spontaneous speech
[171]	Bruyn, 1989, case 20	59/F	I	L	Reduced spontaneous speech
[172]	Ghidoni et al., 1989, case 1	55/F	I	L	Apathy and depression
[173]	Ghidoni et al., 1989, case 2	68/F	I	L	Depression
[176]	Ghidoni et al., 1989, case 5	41/F	I	Bi	Apathy and hypersomnia; depression
[177]	Ghidoni et al., 1989, case 6	52/F	I	L	Character modification (no further information)
[181]	Müller et al., 1989	41/F	I	Bi	Behaviour characterised by indifference, apathy, reduced spontaneous speech
[185]	Graff-Radford et al., 1990, case 1	68/M	I	Bi	Marked personality change: less inhibited
[186]	Graff-Radford et al., 1990, case 2	19/F	I	Bi	Marked personality change: 'she is socially uninhibited and laughs inappropriately'
[202]	Robin and Schienberg, 1990, T2	71/F	I	L	Lethargic behaviour
[213]	Eslinger et al., 1991	58/F	I	Bi	Behaviour characterised by apathy, irritability and occasional aggressive outbursts; utilisation behaviour and occasional agitation required 24-hour supervision by her family
[226]	Rousseaux et al., 1991	41/M	I	R	Lack of initiative
[272]	Cole et al., 1992, case 2	73/F	I	L	Apathy: 'patient spent most of her days lying on the couch, occasionally watching television and rarely going out'

(*continued on next page*)

Appendix 5. (*continued*)

Case	Reference	Age/sex	Aetiology (H/I)	Lesion site	Affective-behavioural description (lesion phase)
[274]	Cole et al., 1992, case 4	72/M	I	L	Apathy: 'impulsion to thought or action was decreased'
[288]	Maeshima et al., 1992	60/F	I	L	Verbal aspontaneity: spoke little of her own volition, no voluntary speech
[289]	Malamut et al., 1992	28/M	I	Bi	Behavioural disturbance characterised by apathy, lack of spontaneity, lack of initiative, abulia; depression and emotional lability
[305]	Baumgartner and Regard 1993, case 1	47/F	I	R	Depression
[306]	Baumgartner and Regard 1993, case 2	46/F	I	R	Depression
[307]	Baumgartner and Regard 1993, case 3	34/F	I	R	Depression
[308]	Baumgartner and Regard 1993, case 4	36/M	I	L	Mildy impaired affect, mood change: irritability and aggression
[312]	Guilleminault et al., 1993, case 2	23/M	I	Bi	Behaviour characterised by extreme hypersomnia with long periods of the day staying motionless in a sleep-like state and intermittent bursts of inappropriate, aggressive, flirtatious behaviour
[313]	Guilleminault et al., 1993, case 3	28/M	I	Bi	Behaviour characterised by extreme hypersomnia with long periods of the day staying motionless in a sleep-like state and intermittent bursts of inappropriate, aggressive, flirtatious behaviour
[314]	Hodges and McCarthy 1993	67/M	I	Bi	Marked personality change: apathetic and lethargic behaviour ('he is content to sit in the house all day watching television'), indifference and lacks insight into his deficits (=anosognosia)
[317]	Kulisevsky et al., 1993	81/F	I	R	DSM III-R: organic affective disorder of the manic type: euphoric, talkative, grandiose delusions, decreased need for sleep
[319]	McGilchrist et al., 1993	43/M	I	Bi	Marked personality change: apathy, hypersomnia altered with excessively eating, hypersexuality, mania and irritability
[321]	Noda et al., 1993, case 2	46/F	I	L	The presence of hallucinations (they became shorter and simpler but did not disappear)
[323]	Pepin and Auray-Pepin, 1993, case 2	57/M	I	R	Change in personality: less talkative, more quiet, unconcerned, lack of initiative, only staying home watching television (apathy), no signs of depression
[327]	Clarke et al., 1994	54/F	I	L	Difficulties in starting a task, lack of motivation, indifference, lack of emotional involvement; emotional lability
[328]	Daum and Ackermann, 1994	63/F	I	Bi	Aspontaneity
[332]	Kotila et al., 1994, case 2	57/M	I	L	Unawareness of memory disturbances
[333]	Kotila et al., 1994, case 3	39/M	I	L	Depression, inactive (apathy) and unawareness of memory disturbances
[334]	Kotila et al., 1994, case 4	41/F	I	L	Inactive (apathy) and unawareness of memory disturbances
[335]	Kotila et al., 1994, case 5	44/M	I	L	Depressive, anxious, psychotic with paranoid ideas, inactive (apathy) and unawareness of memory disturbances
[336]	Kotila et al., 1994, case 6	48/M	I	L	Depressive, anxious, psychotic with paranoid ideas and unawareness of memory disturbances
[337]	Kotila et al., 1994, case 7	50/M	I	L	Depressive, anxious, psychotic with paranoid ideas, inactive (apathy) and unawareness of memory disturbances
[343]	Frey, 1995	63/F	I	Bi	Apathy and loss of initiative

Appendix 5. (*continued*)

Case	Reference	Age/sex	Aetiology (H/I)	Lesion site	Affective-behavioural description (lesion phase)
[344]	Haut et al., 1995	40/F	I	Bi	Limited insight; emotional lability: immature presentation and inappropriate affect
[345]	Luchelli et al., 1995; Luchelli and De Renzi, 1992, case GR	67/M	I	L	Depression, apathy, empty mind: 'no more self to express spending hours sleeping and living in a state of apathy'
[355]	Van Domburg et al., 1996	42/M	I	Bi	Loss of initiative; growing lability of affect: 'he began to talk excessively, sometimes with delusional or annoying expressions'
[357]	Chatterjee et al., 1997	70/F	I	Bi	Apathy: 'she did demonstrate a kind of inertia and did not herself initiate activities, she required considerable supervision and constant encouragement to persist her activities'
[363]	Fung et al., 1997, case 2	48/F	I	Bi	Disinhibition
[386]	Woodman and Tabatabai, 1998	69/M	I	R	Panic disorder: attacks of new-onset episodes of tachycardia, shortness of breath, dizziness, nausea and overwhelming fear of dying, attacks with variable intensities
[393]	Müller et al., 1999	69/F	I	Bi	Marked behavioural alterations: switching between lack of initiative and overactivity; compulsive behaviour, lack of shame, changes in emotional and sexual behaviour
[396]	Van der Werf et al., 1999	44/M	I	R	Inflexible behaviour, apathy ('when left to himself, he will tend not to initiate any activity; he has become apathetic and lethargic'), indifference, lack of initiative, loss of sexual interest
[412]	Karussis et al., 2000, case 13	77/M	I	R	Anosognosia
[413]	Karussis et al., 2000, case 14	38/M	I	R	Anosognosia
[421]	Benabdeljlil et al., 2001	35/F	I	Bi	Anosognosia
[433]	Inzelberg et al., 2001	61/M	I	R	DSM-IV: manic episode by having a distinct period of abnormally and persistently elevated mood, decreased need for sleep, high distractibility, pressured speech and hypersexuality; 2 months postonset: resolved manic episode
[461]	Benke et al., 2002	38/M	I	Bi	Mania with behavioural abnormalities (restlessness, agitation, inappropriate and tactless social behaviour, poor disease awareness) and markedly elevated mood and inflated self-esteem
[464]	Fukutake et al., 2002	48/M	I	L	Egocentric, emotional and behavioural status fluctuating between an irritative (violent), insomniac behaviour and a hypoactive, apathetic state
[465]	Krolak-Salmon et al., 2002	57/M	I	Bi	Behavioural changes: apathy, mental slowing, irritability and lack of insight
[498]	Annoni et al., 2003, case 3	53/M	I	L	Scored anxious on the Hospital Anxiety and Depression Scale
[500]	Annoni et al., 2003, case 5	65/F	I	R	Depression
[528]	Van Der Werf et al., 2003, case 2	31/M	I	R	Impulsivity, disinhibition
[529]	Van Der Werf et al., 2003, case 5	46/F	I	L	Impulsivity, disinhibition
[597]	Mutarelli et al., 2006	63/M	I	Bi	Hypersomnia; abnormal irritability, disinhibition and hypersexuality
[603]	Kuljic-Obradovic et al., 2007	60/M	I	Bi	Persistent personality changes: apathy, lack of insight, lack of spontaneity, indifference

M = male, F = female, H = haemorrhage, I = infarction, L = left thalamic lesion, R = right thalamic lesion, Bi = bilateral thalamic lesion, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders.

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Original articles

The psychology of fatigue in patients with multiple sclerosis: A review

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Abstract

Fatigue is a frequent and disabling symptom in patients with multiple sclerosis (MS), but it is difficult to define and measure. Today, MS-related fatigue is not fully understood, and evidence related to explanatory pathophysiological factors are conflicting. Here, we evaluate the contribution of psychological factors to MS-related fatigue. Insight into the possible underlying psychological mechanisms might help us to develop adequate psychological interventions and to improve the overall management of fatigue. Conceptual issues and the relationships between MS-related fatigue and mood, anxiety, cognition, personality, and cognitive–behavioral factors are discussed, and the implications for clinical practice and research are presented.

Keywords: Cognition; Cognitive–behavioral; Fatigue; Mood; Multiple sclerosis; Personality

Introduction

Multiple sclerosis (MS) is a chronic and unpredictable inflammatory demyelinating disease of the central nervous system (CNS), and it is one of the most common neurological disorders affecting young adults [1]. Consistent with variations in the distribution of pathological white matter lesions in the CNS, the clinical symptoms of MS are diverse and can include visual problems, loss of function or feeling in limbs, bowel and bladder incontinence, and loss of balance. In addition, nonfocal neurological symptoms, such as cognitive and behavioral problems, are frequently reported [2]. Up to 92% of patients with MS complain of fatigue and characterize it as one of the most common and troubling problems [3]. Fatigue can severely affect the ability to perform activities of daily life and is a major reason for unemployment. Therefore, fatigue is related to disability and poor quality of life [4–10].

Although fatigue is a common and troublesome symptom, its pathogenesis is poorly understood. Studies on the etiology of fatigue and reviews about this topic have largely focused on biological factors [11–16]. If fatigue were directly related to the underlying pathophysiology of MS, and thus were a primary somatic manifestation of MS, then we would expect to see a significant relationship between fatigue and disease-related variables. A number of studies have investigated the relationship between fatigue and disease course, disease duration, and neurological impairment, yet no consensus has been reached [13]. Furthermore, several studies failed to establish an association between MS-related fatigue and typical magnetic resonance imaging markers of the disease, such as T_2 lesion load, gadolinium-enhancing lesion activity, and brain atrophy [17–21]. Other studies found significant

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but small relationships using functional neuroimaging techniques [22–26]. Because fatigue often occurs during disease exacerbations and is also reported to be a side effect of disease-modifying medications such as interferon-β, a relationship with autoimmune dysregulation has been suggested [14,27]. However, the results of studies concerning the relationship between MS-related fatigue and pathophysiological mechanisms, including autoimmune and neuroendocrine dysregulation, autonomic system dysfunction, and peripheral muscular mechanisms, are contradictory [28–33] (see Kos et al. [13] for a review of the biological mechanisms of MS-related fatigue).

While one might expect to find a biological explanation for MS-related fatigue, none of the proposed pathophysiological mechanisms can fully explain MS-related fatigue. In this critical review, our aim is to evaluate the contribution of psychological factors to fatigue in MS. In line with findings related to other somatic symptoms [34–37], it is possible that fatigue in MS is determined by psychological factors such as mood, anxiety, and cognitive impairment, which also are common sequelae in MS [38–40]. Furthermore, because it is known that the patients' perception and interpretation of their illness and the way they behave are important predictors of disability [41], it follows that personality and cognitive–behavioral factors could contribute to MS-related fatigue. Insight into the psychological correlates or mechanisms of fatigue might help us to develop adequate interventions and to improve its overall management.

We begin by defining fatigue in MS and by discussing how it is measured. Next, we focus on conceptual issues including the relationships between MS-related fatigue and mood, anxiety, and cognitive impairment, and on the impact of both personality and cognitive–behavioral factors on MS-related fatigue. We conclude with remarks about the implications for clinical practice and future research.

Search strategies

In order to ensure that we presented a complete overview of the potential contribution of psychological factors to fatigue in MS, we identified relevant studies by searching on MEDLINE, PubMed, PsycLIT, and Cochrane databases, and by consulting references from relevant articles (until January 2008). The following searching terms were used: multiple sclerosis, fatigue, tiredness, depression, anxiety, fear, mood, cognition, cognitive, neuropsychological, psychological, personality, coping, neuroticism, emotional instability, negative affect(ivity), illness cognitions, beliefs, catastrophizing, cognitive–behavio(u)ral, and treatment.

Definition and measurement of fatigue in MS

In 1998, the Multiple Sclerosis Council for Clinical Practice Guidelines [42] reached a consensus on the following definition of fatigue in MS: "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities." This definition implies that fatigue is a subjective experience, based on a patient's self-report, and refers to the perception of exhaustion—physically, mentally, or both. The Multiple Sclerosis Council for Clinical Practice Guidelines further differentiated between acute fatigue (newly occurring in the past 6 weeks) and chronic fatigue (lasting longer than 6 weeks).

Chaudhuri and Behan [43] proposed a distinction based on physiology, differentiating between central and peripheral fatigue. Central fatigue, in contrast to neuromuscular or peripheral fatigue, represents a failure to complete physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness. A feeling of constant exhaustion is a characteristic of central fatigue, which is typically seen in MS and might be related to lesions in pathways of arousal and attention, such as the reticular system, the limbic system, and the basal ganglia [44]. However, there is no direct evidence indicating that this mechanism is relevant. Therefore, the distinction between central and peripheral fatigue remains hypothetical, and the definition of fatigue as suggested by the Multiple Sclerosis Council for Clinical Practice Guidelines [42] remains.

Although there are a wide variety of self-report measures for MS-related fatigue (see Christodoulou [45] for an overview), there remains no consensus about clinically relevant, reliable, and responsive outcome measures for fatigue in MS. Given the physical and mental aspects of MS-related fatigue, the measurement should be multidimensional. Questionnaires such as the Multidimensional Fatigue Inventory [46] and the Checklist of Individual Strength [47] have been specifically designed to assess multiple aspects of fatigue, including physical and mental fatigue.

Even though the definition of MS-related fatigue implies self-report, the most obvious problem with self-report questionnaires is their retrospective bias. Several attempts have been made to assess fatigue objectively in order to overcome this limitation [48]. Physical fatigue is measured objectively by quantifying reductions in force, rate, or persistence of motor responses over time or following exposure to some event. Worsening of performance on a mental task over time or after some defined cognitive effort could be used to quantify mental or cognitive fatigue, but there are few studies on this topic [49].

So far, there is only consensus on the definition of MS-related fatigue. In order to facilitate future research, it is important to reach consensus on the method of assessment as well. MS-related fatigue has both physical and mental aspects that can be measured subjectively and objectively. Fatigue in MS, especially the mental aspects of it, is sometimes indistinguishable from feelings of depression, anxiety, or cognitive deficits. Therefore, the concept of fatigue needs to be further evaluated by exploring its possible

relationship with depression and anxiety, as well as with cognition.

The relationship between fatigue and mood/anxiety in MS

Depression is the most common psychiatric disorder in MS, and the estimated prevalence is high, ranging between 27% and 54% [39,50–52]. The association between depression and MS is widely recognized, and it is not surprising to find depressive symptoms in people coping with a chronic and highly variable disease course and an uncertain prognosis [53]. Both psychological adjustment and pathophysiological mechanisms, including impaired mood-influencing biological systems, may underlie the frequency of depression in MS; however, the exact nature of this relationship is complex (see the reviews of Dalton and Heinrichs [53] and Siegert and Abernethy [54] for further depth and details on this topic).

Because fatigue is a common symptom of depression [55], we would expect to see a relationship between fatigue and depression in MS. However, this overlap represents the first methodological problem affecting the validity of assessments for both depression and fatigue. Self-report measures often share the component of fatigue, which might explain the significant relationship between fatigue and depression that has been found in several studies [4,56,57]. Therefore, it has been recommended that fatigue items be removed from depression questionnaires [58,59] or that instruments designed for patients with chronic illnesses—such as the Hospital Anxiety and Depression Scale [60], in which no items assessing somatic symptoms are included—be used for assessment. Using this so-called exclusive approach, a recent cross-sectional study [61] of 739 MS patients reported that subjects with clinically significant depressive symptoms were much more likely to report disabling fatigue. The authors concluded that fatigue is highly sensitive to and specific for clinically significant depressive symptoms, and they recommended screening for depression in MS patients who report disabling fatigue.

Most of the relevant studies have reported significant associations between depression and fatigue [4,8–10,56,57,61–69], although most of these studies were cross-sectional and there were great variations in the assessment methods used. Other studies have found no significant relationship [7,47,70–72], possibly due to small sample sizes [7,71,72].

It is possible that sleep disturbances, also a symptom of depression, could account for the significant relationship between depression and fatigue. Sleep disturbances are common in patients with MS and are often related to the presence of fatigue and depression [73–76]. Although the prevalence of sleep complaints is three times higher in patients with MS than in healthy controls [73], the evidence for disturbed sleep–wake rhythms in these patients are contradictory [77,78]. In addition to depression, several other disease-related factors, including pain and urinary symptoms, can influence the quality of sleep [74,76]. It is possible that sleep disturbances mediate the relationship between depression and fatigue, but there is also evidence indicating that sleep disturbances and depression are independent contributors to fatigue [67]. Strober and Arnett [67] found that both sleep disturbances and depression, together with disease severity, accounted for 43% of the variance, with sleep disturbances being the largest contributor.

While anxiety is a common affective symptom and frequently accompanies depression in MS patients [8,38,79–81], much less attention has been given to its relationship with fatigue than to its relationship with depression. In a recent study on mental and physical fatigue in MS [82], stress was an important correlate of mental fatigue only, while physical activity was an important correlate of physical fatigue, showing the importance of conceptualizing fatigue as multidimensional. However, in the study by Skerrett and Moss-Morris [69], both depression and anxiety were significantly related to mental and physical fatigue. Other studies have found significant but modest associations between anxiety and MS-related fatigue [8,70,81]. Chwastiak et al. [61] did not find a relationship between fatigue and anxiety, but anxiety was assessed by asking a single question about the presence of an anxiety attack in the past month.

On the other hand, the association between both depression and anxiety and fatigue could be the result of the same underlying pathophysiological mechanism, such as the disruption of dopaminergic, histaminergic, and serotonergic pathways [83] and the dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis [84]. Moreover, serotonin levels are influenced by the HPA axis, which in turn interacts with stress and fatigue [85]. In addition, the paradigm of cytokine-induced sickness behavior provides an explanatory mechanism [84,86]. Proinflammatory cytokines that are produced in response to infection induce the development of common symptoms of sickness, such as loss of appetite, sleepiness, withdrawal from normal social activities, and fatigue. This syndrome is defined as sickness behavior and is now recognized as a motivational system that reorganizes the organism's priorities to facilitate recovery from infection [86].

Finally, the use of disease-modifying medications such as interferon-β could put MS patients at a risk for an increase in depressed mood, especially for those with a history of depression [87–89], and this might indirectly cause fatigue. Therefore, it is important to describe patients' characteristics in all studies that focus on fatigue and/or to specify inclusion criteria regarding medication use.

Unfortunately, the studies discussed here were cross-sectional and were not always based on an exclusive approach, complicating interpretation and drawing of conclusion. In addition, longitudinal and randomized controlled studies are needed to infer causality and, in particular,

to gain insight into the direction of influence (i.e., whether depression causes fatigue or visa versa). To the best of our knowledge, there are no available intervention studies that have focused on reduction of fatigue and its effect on depression in patients with MS. As of now, there are only two available intervention studies that have focused on the treatment of depression in MS, and both suggest that fatigue is caused by depression. In the one that investigated the efficacy of group therapy for treating depression in patients with MS, fatigue levels in MS patients declined slightly, whereas fatigue levels of control patients increased during the trial [90]. In the other intervention study, patients received either cognitive–behavioral or supportive group therapy or sertraline, a selective serotonin reuptake inhibitor [91]. While this was an uncontrolled study, its findings also suggest that treatment for depression is associated with reduction in the subjective severity of fatigue symptoms and that this relationship is due primarily to treatment-related changes in mood. In contrast, in their prospective study, Schreurs et al. [68] concluded that the presence of depression did not predict physical or mental fatigue after 1 year, nor was depression predicted by preceding fatigue experiences.

The relationship between fatigue and cognition in MS

As when studying the relationship between fatigue and depression, there is a methodological problem when studying the relationship between fatigue and cognition. Both subjective and objective mental or cognitive fatigue share a component of cognition, either as cognitive performance [49] or as cognitive complaint, such as problems with attention and concentration [46,47]. Therefore, when studying the relationship between mental fatigue and cognition in MS, construct validity is an area of concern.

Similar to depression and anxiety and fatigue, complaints of cognitive dysfunction are often reported by patients with MS [92], and 45–65% of patients show measurable cognitive deficits [93,94]. All cognitive domains can be impaired, but impairment of mental speed, cognitive flexibility, sustained attention, and memory retrieval is quite common in MS [95]. Although MS patients typically report that their cognitive functioning is negatively affected by fatigue [7], there is limited evidence for this relationship. Only two cross-sectional studies have focused on the relationship between fatigue and cognitive complaints in MS [96,97], and their results suggest that fatigue, together with emotional complaints and neurological impairment, contributes to cognitive complaints. In addition, in other populations, noncognitive factors such as mood and anxiety are important correlates of cognitive complaints [98–105].

Furthermore, there is little evidence available on the impact of fatigue on cognitive performance based on neuropsychological assessments. Several studies did not find a relationship between subjective fatigue and cognitive performance [10,106–112]. In some studies, it is possible that no relationship was found because the neuropsychological assessment was reduced to a global screening battery with tasks that required minimal cognitive effort. Such screening batteries might not be appropriate for measuring how fatigue affects cognitive performance. In line with recent evidence in other populations [113–117], it is plausible that fatigue in MS is related to tasks that require sustained attention and executive control. Such tasks are often not assessed in MS patients because they are time consuming and can be enervating for this population. Alternatively, effortful information-processing tasks, such as reaction tests, might depend on fine motor and visual functions, which can also produce noise in the studies.

To overcome the limitations of self-report measures, several techniques have been developed to objectively measure mental fatigue, also referred to as cognitive fatigue [49]. Cognitive fatigue can be conceptualized as a decrease in performance over a prolonged period, such as a working day. Cognitive fatigue can also be viewed as decreased performance during acute but sustained mental effort.

Although several attempts have been made, no study has shown that worsening cognitive functioning over time is a correlate of objective or mental fatigue in MS. In most of the studies [108,110,118–120], prolonged effort produced an increase in the subjective experience of MS-related fatigue, but this increase was not related to a decline in cognitive performance. Jennekens-Schinkel et al. [109] examined reaction times before and after a 4-h neuropsychological evaluation in a group of MS patients and healthy controls. Although both reaction times and subjective fatigue increased in both groups, the magnitude of these changes did not differ between the groups. Other studies [107,119,121] have detected cognitive fatigue in MS, defined as a decrease in performance on tasks for sustained attention. However, only one study [119] could distinguish between MS patients and healthy controls. Because of this lack of specificity and the problem of construct validity, the usefulness of objective measures of fatigue in clinical practice and research is dubious. Even if we can find measures that can sensitively detect objective mental or cognitive fatigue in MS patients, the experience of fatigue must be the starting point in daily clinical practice.

The impact of personality factors

There is substantial evidence indicating that the personality trait of negative affectivity plays an important role in the experience and manifestations of chronic illness [34,37,122]. Negative affectivity, also called neuroticism or emotional instability, is one of the Big Five personality traits and is defined as a stable disposition to experience psychological distress across time and situations [41]. Individuals who score high on questionnaires that assess negative affectivity are likely to interpret bodily sensations in terms of illness, also referred to as the symptom-perception theory [41].

There is some empirical evidence indicating that increased levels of negative affectivity in healthy individuals, as well as in clinical populations [e.g., cancer], predispose individuals to the development or maintenance of fatigue symptoms [123–127]. Likewise, significant relationships between negative affectivity and fatigue have been found in patients with MS [128,129].

Besides negative affectivity, relationships between fatigue and other Big Five personality traits, including (high) conscientiousness and (low) extraversion, have been documented [127,128]. However, the scientific evidence supporting relationships between these traits and fatigue is less clear-cut than that for negative affectivity [127]. Moreover, most of these findings must be interpreted with caution due to the cross-sectional design of the studies, their lack of control groups, and potential confounding by affective comorbidity. Because depression and anxiety are very common in MS, it is likely that these symptoms significantly influence the outcome of personality assessments and, in particular, the level of negative affectivity [130]. Furthermore, MS, like all diseases of the CNS, may affect personality due to underlying pathophysiological changes in the frontal cerebral areas [131,132].

In conclusion, although there is some evidence indicating that personality is related to fatigue in patients with MS, numerous methodological issues preclude drawing definite conclusions at this time.

A cognitive–behavioral perspective

As an extension of the symptom-perception theory [41], a cognitive–behavioral model was recently proposed to explain fatigue and disability levels in patients with MS [69]. In the cognitive–behavioral perspective on fatigue, emphasis is placed on illness cognitions, referring to the way patients think about and interpret their fatigue experience. From this perspective, the individuals' perception of what causes the symptoms, rather than the actual cause of the symptoms, determines their behavior [69]. Although there is evidence indicating that cognitive factors play a less significant role in physical and psychosocial functioning in MS than in CFS [133], others report similar illness cognitions and behavior profiles for both groups of patients [134,135]. In line with studies in other populations [136,137], negative thoughts such as helplessness and somatic attributions have also been found to contribute to both fatigue and disability levels in MS patients [69,138,139]. If fatigue is attributed to a physical illness, patients are more likely to focus on their fatigue and to interpret the consequences of fatigue in a negative way, such as fatigue being a sign of physiological damage [69].

It is plausible that, as in the case of CFS and chronic pain [140–142], these negative illness cognitions in MS patients lead to inadequate responses to their fatigue. Although no causality has been proved, mental fatigue is strongly related to both avoidance resting behavior and all-or-nothing behavior [69]. This means that MS patients who respond to their symptoms by either engaging in excessive rest or avoiding activity, or who push themselves hard when well and then crash are more fatigued and disabled [69].

Although few randomized clinical trials (RCTs) have evaluated the effects of exercise and cognitive–behavioral therapy on fatigue in MS, there is some evidence indicating that physical exercise and behavioral therapy can reduce fatigue [143–146]. One recent RCT found that a multidisciplinary fatigue management program improved the impact of fatigue [147]. The MS patients received energy-saving methods and strategies, psychosocial support, and physiotherapy during four sessions of 2 h each. Surprisingly, the intervention group did not differ from the placebo group that received general information about MS. It is possible that the physiotherapy was insufficiently intensive and its duration was too short to elicit effects different from those resulting from regular daily exercise. Furthermore, it is interesting to note that the placebo intervention also influenced the perceived impact of fatigue and patients' self-efficacy [147]. Self-efficacy—the belief that one can effectively manage a challenging situation—is an important variable in coping with an unpredictable chronic disease and also seems related to fatigue in MS [82].

There is some evidence indicating that exercise training and energy-saving strategies reduce fatigue and increase self-efficacy [145,146]. In patients with MS, the feeling that that they have little control can induce negative cognitions, promoting higher levels of depression and fatigue. Additionally, exercise not only increases endurance and strength but also improves sleep and reduces stress and depressive symptoms in MS patients, thereby preventing a vicious circle [82,144]. These positive effects of exercise contradict the general advice given to MS patients to avoid exercise [148]. Such advice is detrimental because it can contribute to the persistence of fatigue.

In summary, there is increasing evidence indicating that illness cognitions and behavior play significant roles in how patients with MS adjust to fatigue. While it is legitimate for patients with an unpredictable and incurable disabling disease to worry about their health, those patients who are depressed and score high on negative affectivity are especially at risk for negative cognitions [135]. Future research should focus on discerning the cognitive–behavioral mechanisms of MS-related fatigue and on evaluating the efficacy of cognitive–behavioral therapy for MS-related fatigue.

Implications for clinical practice and future research

Chronic fatigue has long been recognized as a major problem for MS patients and has to be seen as a multidimensional experience that can be related to common symptoms such as depression, anxiety, and cognitive impairment. Future longitudinal studies and RCTs in which

fatigue is conceptualized and operationalized multidimensionally are needed in order to clarify the causal relationships between mood, anxiety, cognition, and MS-related fatigue. These studies should (a) use adequate sample sizes; (b) specify the inclusion criteria adequately; (c) control for cointerventions and comorbidities; and (d) use clinically relevant, reliable, and responsive fatigue assessment tools as outcome measures, preferably based on international consent. High-quality studies might help to prevent confusion and provide answers to the very complex problem of fatigue in MS.

MS-related fatigue is probably multifactorial, and it is likely that the relative contributions of the different biological and psychological factors vary in each MS patient who experiences fatigue. However, in clinical practice, MS patients are not helped by having their fatigue validated as an uncontrollable correlate of their disease. Psychological factors can contribute to fatigue reporting and can play a role in its persistence. Patients and healthcare providers should be informed that the way patients perceive and cope with their fatigue could influence how they experience fatigue. Fatigued MS patients should be screened for depression and anxiety, and, when present, these psychiatric comorbidities should be treated. Neuropsychological assessment is recommended when fatigued MS patients experience cognitive complaints. Furthermore, negative fatigue-related thoughts should be detected and adjusted. Physical activity and exercise should be encouraged in general.

Because of the lack of an effective pharmacotherapy for MS-related fatigue [149,150], future strategies for managing fatigue in MS patients should be extended to include psychological screening and treatment, in addition to regular medical therapy, occupational therapy, and physiotherapy. Future research integrating both biological and psychological mechanisms might answer the question of who is at risk for chronic fatigue and might give rise to specific interventions that would help patients to achieve their goals in daily functioning.

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Factors related to difficulties with employment in patients with multiple sclerosis: a review of 2002–2011 literature

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We assess the knowledge available on the difficulties experienced by multiple sclerosis (MS) patients in work-related activities. A literature review was carried out using the keywords 'multiple sclerosis' and 'employment' or 'work' through PubMed and EMBASE. Papers reporting patient-derived data on difficulties at work as primary or secondary outcome measures and published in the period 2002–December 2011 were searched. A total of 26 papers were selected, for a total of 32 507 patients (mean age 46.2 years; 42.1% with relapsing-remitting MS). Most papers reported observational studies or cross-sectional surveys focused on health-related quality of life and MS costs. Symptoms more frequently addressed are fatigue, mobility and cognitive impairments. Limited research has been carried out on the working environment. We found a relatively small number of papers published in the last 10 years on the difficulties that patients with MS can experience at work, and this kind of information always appeared as a secondary outcome. In general, it is possible to affirm that MS has a strong impact on patients' employment status, as the mean unemployment rate was 59%. Research on factors promoting maintenance of remunerative employment is required. ***International Journal of Rehabilitation Research*** **36:105–111 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, whose aetiology is because of an interaction of environmental factors and genetic predisposition, and consists of inflammatory demyelination, axonal loss and formation of sclerotic plaques. The incidence of MS is 4.3/100 000 inhabitants/year (Pugliatti *et al.*, 2006), and prevalence is 54–232/100 000 (Gustavsson *et al.*, 2011), with a weighted average of 105/100 000 considering EU citizens aged 0–65 years: it is higher in northern countries and among young adult women between 20 and 40 years of age (Confavreux and Compston, 2006).

In 80% of the cases, MS presents an acute episode affecting one brain site, with symptoms that may involve motor, sensory, visual and autonomic systems, such as fatigue, weakness, poor balance, bladder dysfunctions, loss of vision, diplopia, dysarthria, impaired speech, affective symptoms, cognitive impairments and motor deficits (Compston and Coles, 2008). The chance of a second episode increases from 50% at 2 years to 82% at 20 years: in this case, the criteria for relapsing-remitting multiple sclerosis (RR-MS) are fulfilled (Fisniku *et al.*, 2008). With time, recovery from each acute episode becomes incomplete, so that patients enter the secondary-progressive phase of MS (SP-MS), whereas for approximately 20% of all MS patients, the illness is progressive from onset [primary-progressive phase of MS (PP-MS)]. In both SP-MS and PP-MS, progression starts at around 40 years (Confavreux and Vukusic, 2006). Given the variety of symptoms that MS patients can experience, the limitations in performing activities are very wide and may deal with mobility (e.g. walking or moving objects), communication or self-care.

The treatment of MS is complex and varies consistently with the different symptoms and disease stages: immunosuppressive treatments to reduce relapse rates and disease activity; corticosteroids for acute stages; GABA-receptor agonists for spasticity; intermittent self-catheterization and oxybutynin for sphincter dysfunction; carbamazepine for paroxysmal attacks; and amantadine for fatigue (Compston and Coles, 2002, 2008). The cost of MS is one of the highest among brain disorders, as it includes direct medical and nonmedical costs (e.g. informal care or accommodation of living places), and indirect costs, that is reduced work productivity and early retirement. The cost per patient/year is estimated at €26 974 (Gustavsson *et al.*, 2011), one-third (i.e. €8725) being indirect costs. Difficulties with employment are a relevant issue in consideration of the variety of symptoms and limitations experienced by MS patients (Simmons, 2010), but the issue of unemployment in MS has only partially been tackled: if, on the one hand, experiences on

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vocational rehabilitation for patients entering or re-entering in the workforce exist, on the other, the issue of maintaining the current employment is not evaluated systematically in research (Townsend, 2008; Varekamp *et al.*, 2008).

Understanding how difficulties with employment and the features of the workplace – including both physical and relational characteristics – interact with MS symptoms is of primary relevance to promote job participation. However, despite the MS high burden and the fact that it affects young individuals of working age, its impact on the individuals' ability to perform work-related activities has not been addressed systematically. This review aimed to assess the knowledge available on the difficulties experienced by MS patients in work-related activities. The influence of demographic and environmental factors such as educational level, social barrier and characteristics of workplace has also been taken into account.

Methods

A literature search was carried out using the keywords 'multiple sclerosis' and 'employment', 'unemployment', 'work' or 'work barrier' through PubMed and EMBASE in the period 2002–December 2011. The main selection criterion was the presence of the selected keywords in the title or in the abstract. Abstracts were read and included if they were clinical trials, RCT or observational quantitative studies in which data on difficulties at work, factors associated or predictors of these difficulties were reported as primary or secondary patient-derived outcome measures. Letters to journals' editors, literature reviews, qualitative papers and papers not in English were excluded.

During checking of abstracts, the most conservative approach possible was used: records were considered for selection also if the information was ambiguous, and the final decision was taken by full-text reading; each abstract and paper was double checked by two blinded reviewers. References of included papers were checked to determine whether other papers, not selected at literature search, could be included.

A synthetic description of the main results of each paper was produced, and descriptive statistics were used to present data. When available, the percentage of patients employed because of MS was derived; the aggregate mean age, disease duration, the median Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983) and percentage of patients with RR-MS were calculated.

Results

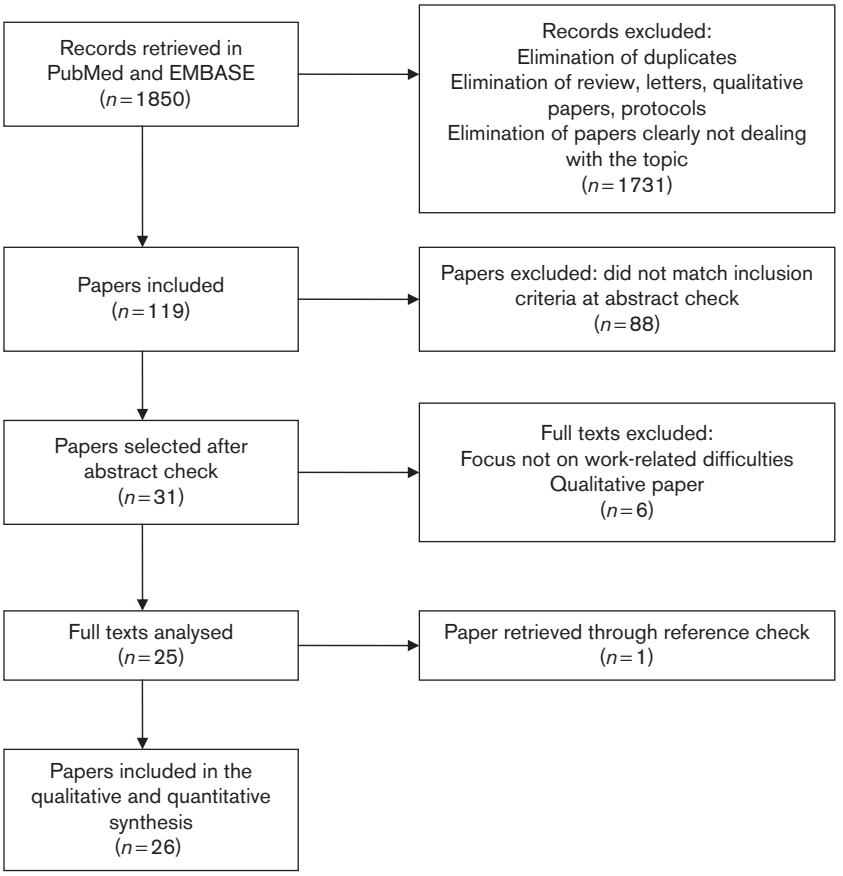
In total, 692 studies were found through PubMed and 1158 through EMBASE. After the elimination of duplicates and of papers not matching the type and topic of study, 119 papers were identified. Of these, 88 were excluded because they did not fulfil the inclusion criteria, mostly for study design, at abstract check, and two more papers were excluded at full-text analysis. One paper was added through a reference check: therefore, 26 papers, reporting data on 32 507 patients, were included in the narrative synthesis (Fig. 1). Most of them were cross-sectional studies on health-related quality of life (HRQoL) and disease costs, whereas patients' ability to perform work duties was frequently addressed as a secondary outcome. Selected papers were mostly European and published between 2005 and 2009. Table 1 provides an overview of the sample of selected papers.

In 2006, the European Journal of Health Economics published a supplement issue on the cost of MS in Europe and patients' HRQoL. The information was collected through a cross-sectional survey: a questionnaire on resource consumption, work capacity, HRQoL and disease status was filled in by a sample of patients recruited through patient organizations and neurology centres (Kobelt *et al.*, 2006h). The research was carried out in nine countries (Berg *et al.*, 2006; Kobelt *et al.*, 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006i): considering all respondents ($n = 13\,417$), 35.8% were employed and 37.4% were early-retired because of MS. Considering only the proportion of patients in the workforce (i.e. those aged <65, $n = 11\,731$), 40.9% were employed and 42.7% were early-retired because of MS. Among employed patients, 32.4% had to reduce the amount of worked hours and 25.8% had to change the type of work following the onset of MS. This study showed that MS had a strong impact on patients' ability to work and the loss of productivity was similar among countries, and that disease progression was consistent with decreased workforce participation and with disease-related costs and HRQoL.

Putzki *et al.* (2009) followed up a cohort of 1149 patients with RR-MS, and found that 14.7% of them were unable to work because of MS and that this inability increased with age. The main predictors of patients' occupational status were baseline EDDS score and duration of MS. HRQoL was related negatively to disease activity and inability to work and related positively to full-time employment. Similar results were found by Patti *et al.* (2007), who analysed the effects of education level and employment status on HRQoL in patients with RR-MS. The results showed that occupation and educational level were significant and independent predictors of HRQoL, thus underlining the importance of maintaining the employment after a recent diagnosis of MS.

A cross-sectional study carried out by Forbes highlighted the correlation between some MS-related problems and HRQoL. The most pervasive effect was exerted by difficulties in relationships and employment: the latter in particular was strongly associated with SF-36's Role Physical scale, which measures problems with work or other daily activities, and Social Functioning scales, which are a measure of the interference of physical and

Fig. 1



Workflow of paper selection.

emotional problems on normal social activities (Forbes *et al.*, 2006). Another cross-sectional survey focused on well-being was carried out by MacLurg *et al.* (2005) using a questionnaire on employment, marital and residential status, receipt of benefits and house modifications: 20% of the patients were employed whereas 56% were retired because of MS, and the employment rates decreased with increasing EDSS.

Julian *et al.* (2008) reported cross-sectional and longitudinal data on employment in 8122 MS patients from the USA. At baseline, 56% of patients were not employed: these were more likely to have a progressive course of disease, longer duration of symptoms, greater disability and functional limitations. After 18 months, 58% were unemployed: those who quit working experienced worsening of symptoms, in particular mobility, hand function, fatigue and cognitive performance. Approximately 5% of patients not employed at baseline started working between baseline and follow-up: these patients had less severe problems in mobility, hand function as well as cognitive functioning, greater levels of education and were younger in age. Similar results were reported by Simmons *et al.* (2010) from an Australian sample: 1135 patients participated in the baseline survey in 2003 (40.3% employed) and 1329 in the follow-up in 2007 (34.9% employed). Men and older patients were more likely to quit working, frequently because of ineffective management of fatigue, mobility-related symptoms and cognitive deficit, rather than because of workplace-related factors.

Messmer Uccelli *et al.* (2009) assessed factors promoting employment in a sample of 1141 MS patients, of whom 61% were employed. Results showed that memory, visual and mobility impairments negatively influenced employment status, whereas flexible work schedules and financial security promoted job maintenance. Furthermore, employed patients were younger and had more years of education. Complementary results were found in a study evaluating the contribution of employment status, age, sex and clinical status towards perceived health status in 184 MS patients, of whom 43.5% were employed: in younger patients, being employed was significantly related to physical and mental health (Krokavcova *et al.*, 2012).

Table 1 Summary characteristics of the studies included

References	Sample size (% women)	Age (mean)	MS type (% RR)	MS duration (mean)	EDSS (median)	Employed (%)	Country
Kobelt *et al.* (2006c)	1019 (70.4%)	50	35.6%	15.3	4.5	34.9%	Austria
Kobelt *et al.* (2006e)	799 (68%)	48.1	38.2%	12.8	4	45.3%	Belgium
Kobelt *et al.* (2006d)	2793 (72.2%)	45.1	39.7%	10.1	4	49.7%	Germany
Kobelt *et al.* (2006b)	921 (65.8%)	46.1	35.4%	12.3	5	46%	Italy
Kobelt *et al.* (2006a)	1549 (69.1%)	46.7	28.9%	9.7	4	40.5%	The Netherlands
Kobelt *et al.* (2006g)	1848 (64.2%)	44.7	37.3%	11.7	5	31.7%	Spain
Berg *et al.* (2006)	1339 (73%)	53.4	21.4%	14.1	6	48.6%	Sweden
Kobelt *et al.* (2006f)	1101 (63.8%)	52.5	29.1%	16.3	5	44.1%	Switzerland
Kobelt *et al.* (2006i)	2048 (74.5%)	51.4	35.5%	12.6	5	31.4%	UK
Putzki *et al.* (2009)	1149 (72.8%)	37.6	100%	3.3	2	90%	Germany
Patti *et al.* (2007)	593 (70.7%)	36.9[a]	100%	3.7[b]	1.5	62.2%	Italy
Forbes *et al.* (2006)	929 (69%)	48	30%	16	–	28%	UK
MacLurg *et al.* (2005)	149 (66%)	51	38%	11.8	6	21%	North Ireland
Julian *et al.* (2008)	8867 (73.9%)	47.6	–	18.1	–	41.1%	USA
Simmons (2010)	2464 (78%)	50.8[a]	–	–	–	49.1%	Australia
Messmer Uccelli *et al.* (2009)	1141 (67%)	41.8	–	–	–	61%	EU countries
Krokavcova *et al.* (2012)	184 (66.3%)	40.5	–	6.4	3	43.4%	Slovakia
Honan *et al.* (2012)	189 (74%)	48.3	66.1%	10.2	–	53.9%	Australia
Morales-Gonzáles *et al.* (2004)	371 (68.7%)	38.9	69.5%	10.2	3.5[c]	33.4%	Spain
Honarmand *et al.* (2011)	103 (77.4%)	44.7	62.3%	9.8	2.5	38.7%	Canada
Busche *et al.* (2003)	96 (65.6%)	47.2	44.8%	14.8	4[c]	52.1%	Canada
Smith and Arnett (2005)	50 (76%)	49.9	56%	10.3	4.5[c]	58%	USA
Riazi *et al.* (2003)	638 (65.3%)	49.1[a]	–	11.6[b]	–	23%	UK
Roessler and Rumrill (2003)	2167 (65.2%)	42.5	–	–	–	–	USA
All studies[d]	32 507 (71.1%)	46.9	42.1%	13.7	–	41%	

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RR-MS, relapsing-remitting multiple sclerosis.
[a]Mean age was derived from categorical data.
[b]Mean duration of disease was derived from categorical data.
[c]Median EDSS was derived from categorical data.
[d]Aggregate mean age, mean percentage of patients with RR-MS and mean MS duration were calculated on the basis of availability of data. The study of Neath *et al.* (2007) is not reported in the table as it is based on the same population of Rumrill *et al.* (2007). The study of Kobelt *et al.* (2006h) is not reported in the table as it presents summary information for references Berg *et al.* (2006) and Kobelt *et al.* (2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006i).

A cross-sectional study carried out by Morales-Gonzáles *et al.* (2004) reported HRQoL information on 371 Spanish MS patients. Patients with progressive forms had a worse quality of life, were more likely to have marital problems, to be separated/divorced because of MS and to be unemployed. They were five-fold more limited in getting around in public places and experienced three-fold greater limitations in social activities.

Honarmand *et al.* (2011) found that employability was strongly predicted by patients' disability status – measured taking into account both physical and cognitive functions – by depression levels and by personality traits such as less extraversion and agreeableness. Being female was also associated with unemployment, whereas educational level was not a predictor.

Busche *et al.* (2003) searched the predictors of unemployment in a group of 96 patients and found that 22% of patients quit working over the 2.5 years, and that the relative risk of becoming unemployed was higher for those older than 40 years of age, with longer duration of disease and with EDSS score greater than 5.5. Education levels and marital status were not associated with employment status.

A cross-sectional study by Smith and Arnett (2005) was the only one that did not find a relationship between employment status, age, sex, cognitive functioning and MS duration. Unemployed MS patients had higher disability and lower education level, experienced more fatigue, and the prestige of their past occupation was lower compared with that of those still working. The factors that contributed considerably toward reducing or quitting working were fatigue and neurological symptoms.

Riazi *et al.* (2003) examined predictors of health status using sociodemographic variables: the results showed that employment was a significant predictor of most of the health dimensions under examination, except mental health and pain. The authors concluded that employment and social class were consistently identified to have some predictive value, but they were deemed to be of limited clinical use.

Two studies (Roessler and Rumrill, 2003; Neath *et al.*, 2007) reported information from the same database composed of 2167 US patients with MS who, between 1992 and 2003, presented a complaint of discrimination at the US Equal Employment Opportunity Commission (EEOC), for a total of 3663 allegations. Roessler and Rumrill (2003) showed that discharge and reasonable accommodation were the most frequent, representing more than 50% of the allegations. Minor sex differences exist: women were more likely to file allegations related to harassment and less likely to file allegations related to hiring or reinstatement; women were more likely to file allegations against employers in service industries and less likely against construction, manufacturing and wholesale industries. Finally, for both sexes, allegations

were more frequent against companies with more than 501 employees. Neath *et al.*, 2007 used a multiple correspondence analysis to determine the most relevant causes of allegations: they concluded that perceived discrimination often originates from employers' failure to provide support and reasonable accommodation or hostility, which can take the shape of harassment, intimidation, layoff and discharge.

Finally, Honan *et al.* (2012) published a validation study of the Multiple Sclerosis Work Difficulties Questionnaire. In this study, they enrolled 189 MS patients, of whom 54% were employed: the instrument indicated 34–40% of issues related to work reduction, cessation or change in work type. In this study, employed patients had completed more years of education.

Discussion

This review aimed to assess the available knowledge on work-related difficulties experienced by MS patients, accounting for MS symptoms and for the influence of educational level, social barrier and characteristics of workplace. The symptoms that have frequently been reported to reduce MS patients' ability to work are fatigue, mobility impairments and cognitive impairments. In contrast, limited research has been carried out on workplace environment and the variables used to assess patients' problem with employment were always the secondary outcome: therefore, there was no study specifically addressing the issue of work-related difficulties and of the factors promoting patients' ability to fulfil job requirements. Analysis of sociodemographic factors showed that unemployed patients were older, had a lower educational level and lower prestige in their past work. In general, it is possible to affirm that MS determines a strong impact on patients' employment status: the aggregate mean unemployment rate was in fact 59%.

Fatigue is the most frequently reported symptom in the papers included in the present review (Forbes *et al.*, 2006; Julian *et al.*, 2008; Simmons *et al.*, 2010). It is linked to occupational status, increasing the likelihood of losing a job, reducing worked hours or changing the type of work activity. Fatigue is a very common symptom in MS that can have a major impact on HRQoL. However, as it is a subjective experience, it can be difficult to measure (Johnson, 2008) and might be misinterpreted for laziness in the context of the workplace. Its assessment is therefore of primary relevance, as there is some evidence of the efficacy of different kinds of fatigue-targeted interventions, including medications, physical activity, energy conservation and cognitive-behavioural therapy (Krupp *et al.*, 2010).

Some papers (Julian *et al.*, 2008; Messmer Uccelli *et al.*, 2009; Simmons *et al.*, 2010) have also reported that mobility problems (e.g. problems with legs or feet, difficulties in getting around and reaching some places) and cognitive difficulties (e.g. memory, concentration and thinking difficulty) determine increased problems with employment. Patients with these symptoms are more likely to leave their job or require changes at work. This issue is very relevant because, as shown in the 2006 issue of the *European Journal of Health Economics* (Berg *et al.*, 2006; Kobelt *et al.*, 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006h, 2006i), 25.8% of employed MS patients had to change their work tasks and 32.4% had to reduce the number of working hours.

Other symptoms linked to losing job or changes at work are hand function (Julian *et al.*, 2008; Simmons *et al.*, 2010), visual impairment (Messmer Uccelli *et al.*, 2009) and pain (Forbes *et al.*, 2006), but their impact is limited, compared with fatigue, mobility and cognitive difficulties.

Inability to work was found to increase consistently with the severity and duration of disease (MacLurg *et al.*, 2005; Berg *et al.*, 2006; Kobelt *et al.*, 2006a, 2006b, 2006c, 2006d, 2006e, 2006f, 2006g, 2006i; Julian *et al.*, 2008; Putzki *et al.*, 2009). Parallel to this, there is some evidence that being employed is related to HRQoL and perceived health in particular among younger patients (Forbes *et al.*, 2006; Patti *et al.*, 2007; Putzki *et al.*, 2009; Krokavcova *et al.*, 2012). For this reason, we believe that research should focus on factors that promote employment in MS patients, as these factors are poorly addressed in research. Evidence that flexible work schedule and financial security are key factors that promote job maintenance has been reported only by Messmer Uccelli *et al.* (2009), whereas the role of ineffective symptoms management, rather than factors related to the workplace, as the main reason for quit working was reported by Simmons *et al.* (2010). Two studies have reported the most frequent discriminations among patients with MS and have identified the causes in the employer's inability to provide support and reasonable accommodation and in their hostility, such as harassment, intimidation, layoff and discharge (Neath *et al.*, 2007; Rumrill *et al.*, 2007).

Previous research (Roessler and Rumrill, 2003) concluded that there are several explanations for the high unemployment in patients with MS, and that the most practical and effective approach to improve employment outcome is to improve organisational and physical workplace features. This is consistent with the biopsychosocial perspective that recognizes the relevance of the person–environment interaction. Our results show that considerable research has been carried out on the 'person' side, whereas much is to be done on the 'environment' side.

Some limitations need to be acknowledged. Even though our search was extensive, we cannot be sure that all relevant articles were located. The fact that factors promoting job maintenance are poorly represented is likely because of the fact that, between 2002 and 2011, the issue of remunerative employment was mostly addressed in

terms of disease burden and cost rather than possible determinants of outcomes. However, expanding the search period for more years would have made little sense, as the labour and welfare situation of the 1980s or 1990s were considerably different, from an economic perspective or taking into account working modalities, for example with the diffusion of informatics platforms. A comment should be made on selected search terms. We decided to rely on the widest possible strategy, using 'work', 'employment', 'work barrier' and 'unemployment' as search terms: this determined that several papers were retrieved through a literature search, but the vast majority of them contained the key word 'work' with a profoundly different meaning (e.g. trials in which work was used to address the fact that a given pharmacological agent was effective or not). Finally, the heterogeneity across studies also has to be taken into account. The studies were very different with respect to sample size, patients' age and clinical features of MS (e.g. RR-MS varied between 21.4 and 100%).

Conclusion

We found a relatively small number of papers published in the last 10 years on the difficulties that patients with MS can experience at work, and this kind of information always appeared as a secondary outcome. Most of the papers investigated factors determining quality of life and its link to employment, and factors that are correlated with employment status or early retirement. Approximately 59% of MS patients are unemployed, and the rate increases consistently with increased patients' age and disease duration. Fatigue, mobility impairments and cognitive impairments were reported as the main drivers of job-related difficulties, whereas employer's hostility and lack of support and accommodations were identified as the cause of perceived discriminations. Factors promoting employment are scarcely reported, and are generally referred to flexible work schedule and financial security. Studies that specifically address patients' difficulties and the determinants of such difficulties are needed. Rehabilitation counselling is needed to reduce the effect of stigma by employers and coworkers, and to support patients with MS to identify and express their needs and to find appropriate accommodations in their workplace. This kind of intervention could ensure adequate levels of performance and the maintenance of employment (Neath *et al.*, 2007).

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Conflicts of interest

There are no conflicts of interest.

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Research Publications

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Research Presentations

Guarnaccia J. Daptomycin Treatment in Progressive and Relapsing Multiple Sclerosis. Poster presentation at ACTRIMS meeting. July, 2010. San Antonio. TX

Guarnaccia JB, Kazis L, Kashner TM, Collins D, O'Connor T, Hope MA, Brennan J, Booss J. Costs, Quality of Life and Functional Outcomes of Veterans with Multiple Sclerosis Treated with Interferon Beta. Platform presentation at the Consortium of Multiple Sclerosis Centers Annual Meeting. Calgary, Alberta. September 5-7, 1997.

Guarnaccia J, MD, Marek K, MD, Solimena M, MD, DeCamilli P, MD. Clinical and Biochemical Features of Stiffman Syndrome. Platform presentation at the Movement Disorders Symposium of the American Neurological Association annual meeting. Boston, MA, October, 1993.

Guarnaccia J, MD, Whang R, MD, Sinha R, PhD. Ethical Decision-making: Differences in Values Among Internists. Poster presented at the Oklahoma Chapter of the American College of Physicians, Lake Eufaula, Oklahoma, October, 1989.

Guarnaccia J, MD, Whang R, MD, Sinha R, PhD. Ethical Decision-making: Differences in Values Among Internists. Poster presentation at the Oklahoma Association of House Staff Physicians, Oklahoma City, Oklahoma, May, 1989. Second prize awarded.

Guarnaccia, J, MD, Makintubee S, MS, Istre G, MD, Slater L, MD. Adolescent and adult cases of Haemophilus influenzae disease in Oklahoma, 1985-1986. Paper presented at the joint meeting of the Oklahoma Society of Internal Medicine and Oklahoma Chapter of the American College of Physicians, Shangri La, Oklahoma, October, 1987.

Guarnaccia J, MD, Makintubee S, MS, Istre G, MD, Slater L, MD. Adolescent and adult cases Haemophilus influenzae disease in Oklahoma, 1985-1986. Paper presented at the Central Society for Clinical Research, regional meeting of the American College of Physicians. Chicago, Illinois, November, 1986.

Awards and Memberships

1998, July	Multiple Sclerosis Representative on a VA Neurology Task Force on Clinical Research Trials.
1998 to present	VA Spinal Cord Registry Product Improvement Member. An advisory group that meets monthly to revise and improve the spinal cord registry.
1998	Voted "Best Doctors in Connecticut," Connecticut Magazine Survey
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1995 to present	Member Expert Panel on the VA Spinal Cord Registry: sponsored jointly by PVA and HSRD. VAMC, Durham, NC
1993 to present	Trustee Greater Connecticut Chapter of the National Multiple Sclerosis Society Professional Advisory Committee, Greater Connecticut Chapter and Western Connecticut Chapter National Multiple Sclerosis Society
1993 to present	Connecticut Neurological Society
1992 to 1993	Working committee on resident/student education. Department of Neurology, Yale University
1992 to 1993	Committee on Quality Assurance. Yale New Haven Hospital
1992-1993	Organizer. Resident Noon Conference Lecture Series. Department of Neurology
1990	Ethics Committee. VA Medical Center, Oklahoma City

1987	Presbyterian Harris Health Foundation Student Research Scholarship Award

Research

April, 2013	Principal Investigator. A clinical evaluation of the safety of baclofen ER capsules (GRS) when administered once daily to subjects with spasticity due to multiple sclerosis (MS): An open label, long term safety trial. Sun Pharmaceuticals.
September, 2012	Principal Investigator. A placebo-controlled, randomized withdrawal evaluation of the efficacy and safety of baclofen ER capsules (GRS) in subjects with spasticity due to multiple sclerosis. Sponsor: Sun Pharmaceuticals.
February, 2010	Principal Investigator. JCV Antibody Program in Patients with Relapsing Multiple Sclerosis Receiving or Considering Treatment with Tysabri: STRATIFY-2.
February, 2002	Principal Investigator, Randomized, parallel group, open label study comparing the tolerability of Rebif injection with or without the use of the Rebiject™ mini autoinjector. Sponsored by Serono, Inc.
January, 2002	Principal Investigator, Double blinded, placebo controlled study of Natalizumab added to Avonex in subjects with relapsing-remitting multiple sclerosis. Phase III study sponsored by Biogen, Inc.
November 2000	Principal Investigator. Controlled High Risk AVONEX® (Interferon Beta-1a) Multiple Sclerosis Prevention Study in On-going Neurological Surveillance. Phase IV study sponsored by Biogen, Inc.
1998 to 1999	Principal Investigator. Treatment of patients with relapsing remitting MS with 3 doses of CGP77116 vrs. Placebo. Phase II study enrolling 10 or more patients. Sponsored by Novartis.
1998 to 1999	Principal Investigator. Phase III study of Interferon 1a in the Treatment of Patients with Secondary Progressive Multiple Sclerosis. Two year study. Sponsored by Biogen.

1997 to 1998	Principal Investigator. A Tolerability Study of AVONEX (Interferon beta-1a) in the Treatment of Subjects with Relapsing and Secondary Progressive Multiple Sclerosis. Phase II clinical study with 12 patients enrolled. One year duration.
1996 to present	Principal Investigator. HSR&D Project SDR#91-001 "Costs and Quality of Life and Functional Outcomes in Veterans Treated for Multiple Sclerosis with Beta Interferon 1-B (Betaseron)." Three year grant of $422,000 awarded August, 1996.
1996 to June, 2000	Co-principal Investigator. Nancy Davis Center Without Walls. Research consortium of five academic MS Centers (UCSF, UCLA, U. of Portland, CNND, Brigham & Women's Hospital, Yale MS Center) funded by the Nancy Davis Foundation, Los Angeles, CA, to conduct collaborative research in multiple sclerosis.
1996 to 2000	Principal Investigator. Use of Interferon Beta-1a (AVONEX) to Treat Patients with an Initial Demyelinating Event and an MRI which shows High Risk of Development of Clinically Definite MS. Three-year, multi-center clinical study.
1995 to present	Principal Investigator. Use of Cladribine to treat Patients with Chronic Progressive or Relapsing Progressive Multiple Sclerosis. Seven-year, multi-center clinical study involving thirty patients at Yale.
1993 to 1995	Principal Investigator. Total Lymphoid Irradiation in the Treatment of Chronic Progressive Multiple Sclerosis. Twenty-four patients with multiple sclerosis enrolled in a three-year clinical trial.
1993 to 1994	Principal Investigator. Immunological Studies in Patients with Multiple Sclerosis. Collaboration with Immunologic Pharmaceutical Corp., Palo Alto, CA.
1993 to June, 2000	Principal Investigator. Cop-1 in the treatment of Patients with Relapsing-Remitting Multiple Sclerosis. Open label clinical study.

1993 to 1994	Co-investigator. Plasma Exchange Versus Sandoglobulin Guillain-Barre Syndrome Trial. Two-year, international multi-center trial.
January, 1987 to March, 1987	Presbyterian Harris Research Scholar. Investigation of Haemophilus influenzae infections in adults in Oklahoma. Statewide record reviews and testing of bacterial isolates provided by the Oklahoma State Health Department.
January, 1981 to July, 1983	Assistant in the laboratory of Paul Bell, PhD, Cell Biology, University of Oklahoma, Norman. Investigated mouse hybridoma model for melanoma.

Lectures

2013, November	New developments in MS therapies. Grand Rounds, Norwalk Hospital, Norwalk, CT
2013, September	Treatment Paradigms for Multiple Sclerosis. NE Pharmacists Convention. Foxwoods Casino, CT
2011, October	"Antibiotic Treatment of Multiple Sclerosis with Minocycline and Daptomycin." European Charcot Foundation . Satellite Symposium entitled "Bowel and Brain." October 19, 2011. Ectrims 2011. Amsterdam, Holland
2011, September	Treatment Paradigms for Multiple Sclerosis. NE Pharmacists Convention. September 16th, 2011. Foxwoods Casino, CT
2004, January	Symptom Management in Multiple Sclerosis. CME Presentation, "Advancing Trends in Multiple Sclerosis Disease Management, January 31, 2004, sponsored by the University of South Florida.
2001, January	"Advanced Strategies in the Treatment of Multiple Sclerosis." Live Interactive Patient Teleconference. Sponsored by Berlex Laboratories Inc.
2000, November	"In Depth Presentation of the CHAMPS study data." Grand Rounds. St. Luke's Hospital. Bethlehem, PA

1998, May	"Multiple Sclerosis - treatment update." Western Massachusetts Hospital. Sturbridge.
1998, April	"Advances in the Treatment of MS." Grand Rounds. St. Raphael's Hospital.
1997, October	"Current Research and Medical Therapies for MS." Annual Meeting, Western Connecticut Chapter MS Society, Norwalk, CT.
1997, October	"Therpeutic Use of Interferons in Multiple Sclerosis." Allergy & Clinical Immunology Series, Yale University.
1997, September	"Multiple Sclerosis - Overview and Treatment." Newly Diagnosed Group Meeting. Sponsored by the Western Connecticut Chapter MS Society. Norwalk, CT.
1997, February	"Multiple Sclerosis." Medical Grand Rounds. Greenwich Hospital.
1996, October	"Current Clinical Trials in Multiple Sclerosis." Forum sponsored by the Massachusetts MS Society, Sturbridge, MA.
1996, September	"VA Spinal Cord registry." Workshop at the Annual Meeting, Consortium of Multiple Sclerosis Centers, Atlanta, Georgia.
1996, August	"Use of Cladribine in Multiple Sclerosis." Rounds center for Neurological Diseases, Brigham and Women's Hospital, Boston, MA.
1996, April	"Multiple Sclerosis – Diagnosis and Treatment." Medical Grand Rounds, St. Vincent's Hospital, Bridgeport, CT.
1995, January	"CNS Angitis." Rheumatology Grand Rounds, Yale New Haven Hospital.